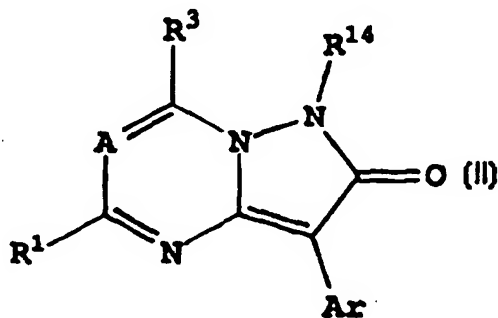
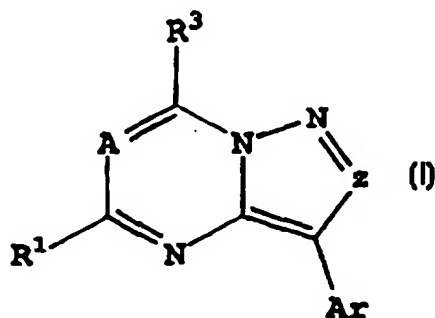




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| <p>(21) International Application Number: PCT/US97/13072</p> <p>(22) International Filing Date: 23 July 1997 (23.07.97)</p> <p>(30) Priority Data:</p> <table border="0"> <tr> <td>60/023,290</td> <td>24 July 1996 (24.07.96)</td> <td>US</td> </tr> <tr> <td>08/686,047</td> <td>24 July 1996 (24.07.96)</td> <td>US</td> </tr> <tr> <td>Not furnished</td> <td>23 July 1997 (23.07.97)</td> <td>US</td> </tr> </table> <p>(71) Applicant: THE DU PONT MERCK PHARMACEUTICAL COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US).</p> <p>(72) Inventors: ARVANITIS, Argyrios, Georgious; 101 Willow Glen Drive, Kennett Square, PA 19348 (US). CHORVAT, Robert, John; 1193 Killamey Lane, West Chester, PA 19382 (US).</p> <p>(74) Agent: FERGUSON, Blair, Q.; The du Pont Merck Pharmaceutical Company, Legal/Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).</p> | | 60/023,290 | 24 July 1996 (24.07.96) | US | 08/686,047 | 24 July 1996 (24.07.96) | US | Not furnished | 23 July 1997 (23.07.97) | US | <p>(81) Designated States: AM, AU, AZ, BR, BY, CA, CN, CZ, EE, HU, IL, JP, KG, KR, KZ, LT, LV, MD, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, UA, VN, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> |
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(54) Title: AZOLO TRIAZINES AND PYRIMIDINES



(57) Abstract

Corticotropin releasing factor (CRF) antagonists of formula (I) or (II) and their use in treating anxiety, depression, and other psychiatric, neurological disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.

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TITLE

AZOLO TRIAZINES AND PYRIMIDINES

5

FIELD OF THE INVENTION

This invention relates a treatment of psychiatric disorders and neurological diseases including major depression, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress, by administration of certain [1,5-a]-pyrazolo-1,3,5-triazines, [1,5-a]-1,2,3-triazolo-1,3,5-triazines, [1,5-a]-pyrazolo-pyrimidines and [1,5-a]-1,2,3-triazolo-pyrimidines.

20

BACKGROUND OF THE INVENTION

Corticotropin releasing factor (herein referred to as CRF), a 41 amino acid peptide, is the primary physiological regulator of proopiomelanocortin(POMC)-derived peptide secretion from the anterior pituitary gland [J. Rivier et al., *Proc. Nat. Acad. Sci. (USA)* 80:4851 (1983); W. Vale et al., *Science* 213:1394 (1981)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in brain [W. Vale et al., *Rec. Prog. Horm. Res.* 39:245 (1983); G.F. Koob, *Persp. Behav. Med.* 2:39 (1985); E.B. De Souza et al., *J.*

Neurosci. 5:3189 (1985)). There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, *Physiological Reviews* 69:1 (1989); J.E. Morley, *Life Sci.* 41:527 (1987)].

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, *Hosp. Practice* 23:59 (1988)].

In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebral spinal fluid (CSF) of drug-free individuals [C.B. Nemeroff et al., *Science* 226:1342 (1984); C.M. Banki et al., *Am. J. Psychiatry* 144:873 (1987); R.D. France et al., *Biol. Psychiatry* 28:86 (1988); M. Arato et al., *Biol Psychiatry* 25:355 (1989)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., *Arch. Gen. Psychiatry* 45:577 (1988)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., *Am J. Psychiatry* 141:619 (1984); F. Holsboer et al., *Psychoneuroendocrinology* 9:147 (1984); P.W. Gold et al., *New Eng. J. Med.* 314:1129 (1986)]. Preclinical studies in rats and non-human primates provide additional support for the

hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (1989)].

There is preliminary evidence that tricyclic
5 antidepressants can alter CRF levels and thus modulate the numbers of CRF receptors in brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (1989)].

There has also been a role postulated for CRF in
10 the etiology of anxiety-related disorders. CRF produces anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety
15 models [D.R. Britton et al., *Life Sci.* 31:363 (1982); C.W. Berridge and A.J. Dunn *Regul. Peptides* 16:83 (1986)]. Preliminary studies using the putative CRF receptor antagonist α -helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the
20 antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn *Horm. Behav.* 21:393 (1987), *Brain Research Reviews* 15:71 (1990)].

Neurochemical, endocrine and receptor binding studies
25 have all demonstrated interactions between CRF and benzodiazepine anxiolytics providing further evidence for the involvement of CRF in these disorders.

Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton et
30 al., *Psychopharmacology* 86:170 (1985); K.T. Britton et al., *Psychopharmacology* 94:306 (1988)] and in the acoustic startle test [N.R. Swerdlow et al., *Psychopharmacology* 88:147 (1986)] in rats. The benzodiazepine receptor antagonist (Ro15-1788), which
35 was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-

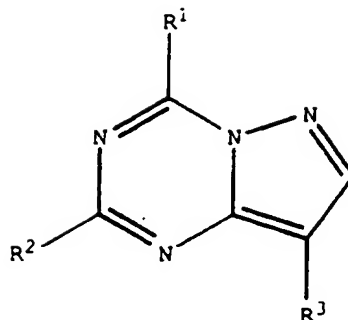
dependent manner while the benzodiazepine inverse agonist (FG7142) enhanced the actions of CRF [K.T. Britton et al., *Psychopharmacology* 94:306 (1988)].

The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist (α -helical CRF9-41) in a variety of behavioral paradigms have demonstrated that the CRF antagonist produces "anxiolytic-like" effects qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: *Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)].

Several publications describe corticotropin releasing factor antagonist compounds and their use to treat psychiatric disorders and neurological diseases. Examples of such publications include DuPont Merck PCT application US94/11050, Pfizer WO 95/33750, Pfizer WO 95/34563, Pfizer WO 95/33727 and Pfizer EP 0778 277 A1.

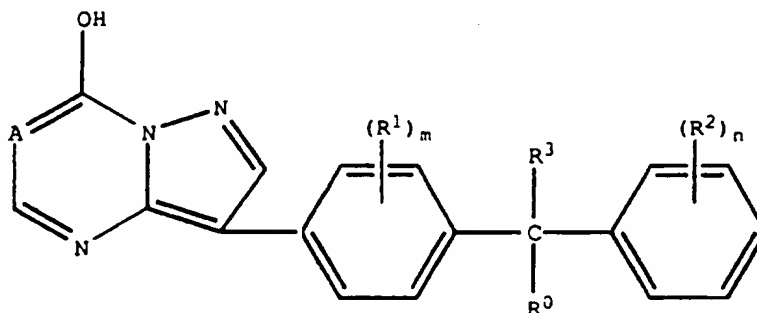
Insofar as is known, [1,5-a]-pyrazolo-1,3,5-triazines, [1,5-a]-1,2,3-triazolo-1,3,5-triazines, [1,5-a]-pyrazolo-pyrimidines and [1,5-a]-1,2,3-triazolo-pyrimidines, have not been previously reported as corticotropin releasing factor antagonist compounds useful in the treatment of psychiatric disorders and neurological diseases. However, there have been publications which teach some of these compounds for other uses.

For instance, EP 0 269 859 (Ostuka, 1988) discloses pyrazolotriazine compounds of the formula



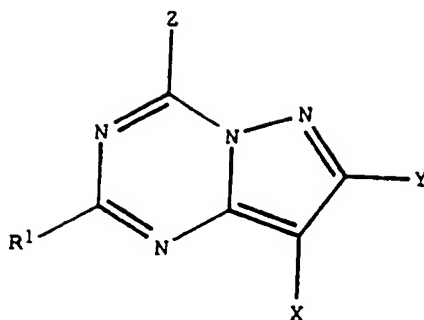
where R^1 is OH or alkanoyl, R^2 is H, OH, or SH, and R^3 is
 5 an unsaturated heterocyclic group, naphthyl or substituted phenyl, and states that the compounds have xanthine oxidase inhibitory activity and are useful for treatment of gout.

10 EP 0 594 149 (Ostuka, 1994) discloses pyrazolotriazine and pyrazolopyrimidine compounds of the formula



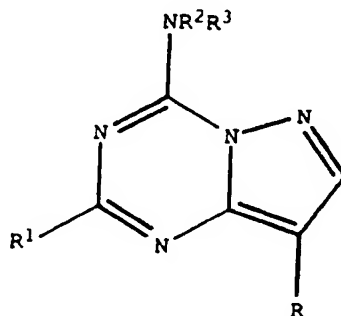
15 where A is CH or N, R^0 and R^3 are H or alkyl, and R^1 and R^2 are H, alkyl, alkoxyl, alkylthio, nitro, etc., and states that the compounds inhibit androgen and are useful in treatment of benign prostatic hypertrophy and
 20 prostatic carcinoma.

US 3,910,907 (ICI, 1975) discloses pyrazolotriazines of the formula:



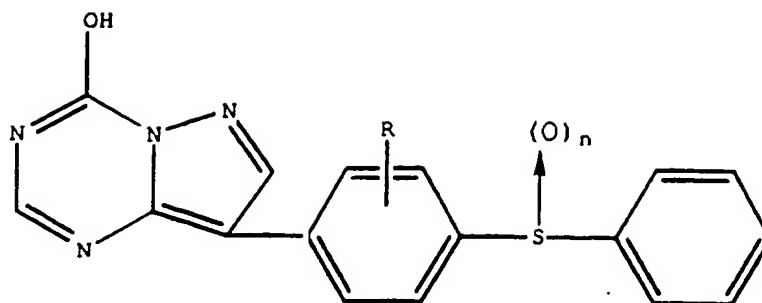
where R¹ is CH₃, C₂H₅ or C₆H₅, X is H, C₆H₅, m-CH₃C₆H₄, CN, COOEt, Cl, I or Br, Y is H, C₆H₅, o-CH₃C₆H₄, or p-CH₃C₆H₄, and Z is OH, H, CH₃, C₂H₅, C₆H₅, n-C₃H₇, i-C₃H₇, SH, SCH₃, NHC₄H₉, or N(C₂H₅)₂, and states that the compounds are c-AMP phosphodiesterase inhibitors useful as bronchodilators.

10 US 3,995,039 discloses pyrazolotriazines of the formula:



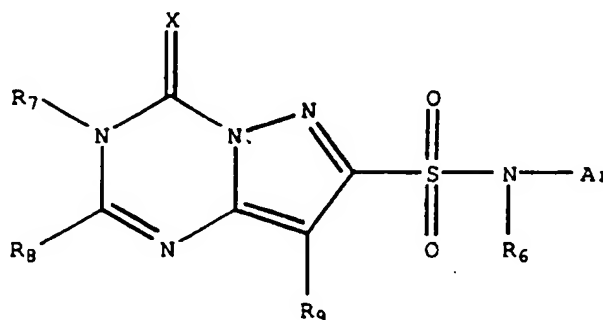
15 where R¹ is H or alkyl, R² is H or alkyl, R³ is H, alkyl, alkanoyl, carbamoyl, or lower alkylcarbamoyl, and R is pyridyl, pyrimidinyl, or pyrazinyl, and states that the compounds are useful as bronchodilators.

20 US 5,137,887 discloses pyrazolotriazines of the formula



where R is lower alkoxy, and teaches that the compounds
are xanthine oxidase inhibitors and are useful for
5 treatment of gout.

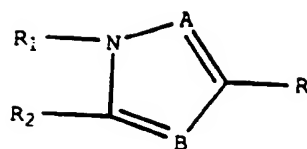
US 4,892,576 discloses pyrazolotriazines of the
formula



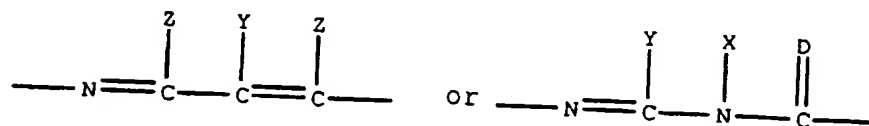
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where X is O or S, Ar is a phenyl, naphthyl, pyridyl or
thienyl group, R₆-R₈ are H, alkyl, etc., and R₉ is H,
alkyl, phenyl, etc. The patent states that the
15 compounds are useful as herbicides and plant growth
regulants.

US 5,484,760 and WO 92/10098 discloses
herbicidal compositions containing, among other things,
20 a herbicidal compound of the formula

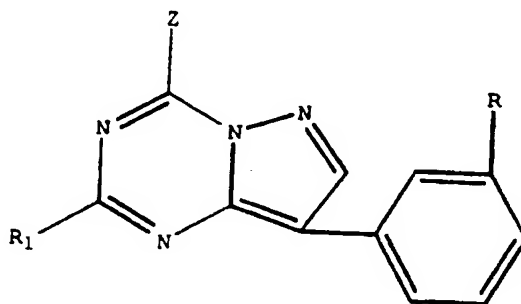


where A can be N, B can be CR₃, R₃ can be phenyl or substituted phenyl, etc., R is -N(R₄)SO₂R₅ or -SO₂N(R₆)R₇ and R₁ and R₂ can be taken together to form



where X, Y and Z are H, alkyl, acyl, etc. and D is O or S.

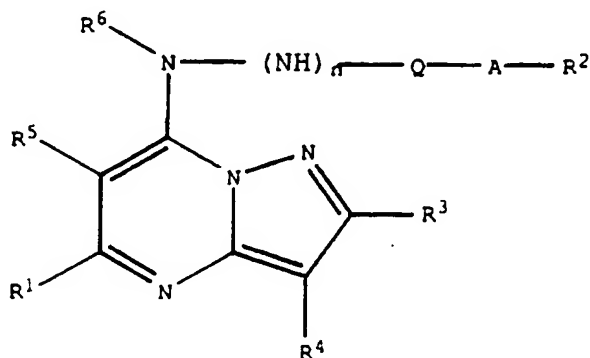
US 3,910,907 and Senga et al., J. Med. Chem., 1982, 25, 243-249, disclose triazolotriazines cAMP phosphodiesterase inhibitors of the formula



where Z is H, OH, CH₃, C₂H₅, C₆H₅, n-C₃H₇, iso-C₃H₇, SH, SCH₃, NH(n-C₄H₉), or N(C₂H₅)₂, R is H or CH₃, and R₁ is CH₃ or C₂H₅. The reference lists eight therapeutic areas where inhibitors of cAMP phosphodiesterase could have utility: asthma, diabetes mellitus, female fertility control, male infertility, psoriasis, thrombosis, anxiety, and hypertension.

WO95/35298 (Otsuka, 1995) discloses pyrazolopyrimidines and states that they are useful as analgesics. The compounds are represented by the formula

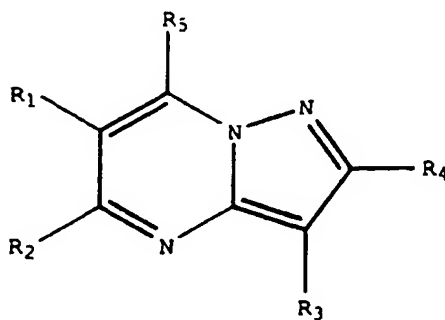
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where Q is carbonyl or sulfonyl, n is 0 or 1, A is a single bond, alkylene or alkenylene, R¹ is H, alkyl, etc., R² is naphthyl, cycloalkyl, heteroaryl, substituted phenyl or phenoxy, R³ is H, alkyl or phenyl, R⁴ is H, alkyl, alkoxycarbonyl, phenylalkyl, optionally phenylthio-substituted phenyl, or halogen, R⁵ and R⁶ are H or alkyl.

15

EP 0 591 528 (Otsuka, 1991) discloses anti-inflammatory use of pyrazolopyrimidines represented by the formula

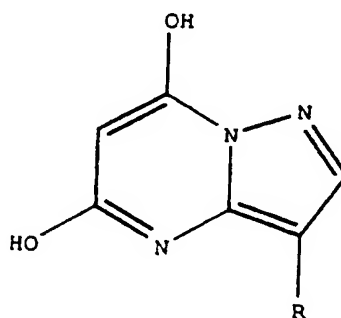


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where R₁, R₂, R₃ and R₄ are H, carboxyl, alkoxycarbonyl, optionally substituted alkyl, cycloalkyl, or phenyl, R₅

is SR_6 or NR_7R_8 , R_6 is pyridyl or optionally substituted phenyl, and R_7 and R_8 are H or optionally substituted phenyl.

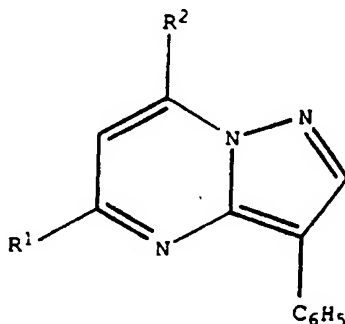
- 5 Springer et al, J. Med. Chem., 1976, vol. 19, no. 2, 291-296 and Springer U.S. patents 4021,556 and 3,920,652 disclose pyrazolopyrimidines of the formula



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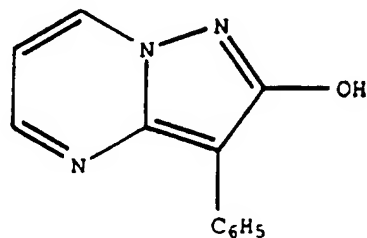
where R can be phenyl, substituted phenyl or pyridyl, and their use to treat gout, based on their ability to inhibit xanthine oxidase.

- 15 Joshi et al., J. Prakt. Chemie, 321, 2, 1979, 341-344, discloses compounds of the formula



- 20 where R^1 is CF_3 , C_2F_5 , or C_6H_4F , and R^2 is CH_3 , C_2H_5 , CF_3 , or C_6H_4F .

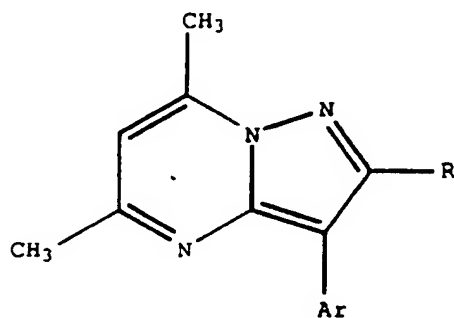
Maquestiau et al., Bull. Soc. Belg., vol.101, no. 2, 1992, pages 131-136 discloses a pyrazolo[1,5-a]pyrimidine of the formula



5

Ibrahim et al., Arch. Pharm. (weinheim) 320, 487-491 (1987) discloses pyrazolo[1;5-a]pyrimidines of the formula

10



where R is NH₂ or OH and Ar is 4-phenyl-3-cyano-2-aminopyrid-2-yl.

15

Other references which disclose azolopyrimidines included EP 0 511 528 (Otsuka, 1992), US 4,997,940 (Dow, 1991), EP 0 374 448 (Nissan, 1990), US 4,621,556 (ICN,1997), EP 0 531 901 (Fujisawa, 1993), US 4,567,263 (BASF, 1986), EP 0 662 477 (Isagro, 1995), DE 4 243 279 (Bayer, 1994), US 5,397,774 (Upjohn, 1995), EP 0 521 622 (Upjohn, 1993), WO 94/109017 (Upjohn, 1994), J. Med. Chem., 24, 610-613 (1981), and J. Het. Chem., 22, 601 (1985).

25

SUMMARY OF THE INVENTION

In accordance with one aspect, the present invention provides novel compounds, pharmaceutical compositions and methods which may be used in the treatment of affective disorder, anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other feeding disorder, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorder, fertility problems, disorders, the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic, phobias, obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthymia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer, human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases such as ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ileus and colonic hypersensitivity associated by psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress;

stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g.,
5 cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and hear related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress
10 induced immune dysfunctions (e.g., stress induced fevers, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction
15 related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin,
20 benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia in a mammal.

The present invention provides novel compounds
25 which bind to corticotropin releasing factor receptors, thereby altering the anxiogenic effects of CRF secretion. The compounds of the present invention are useful for the treatment of psychiatric disorders and neurological diseases, anxiety-related
30 disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and
35 stress in a mammal.

According to another aspect, the present invention provides novel compounds of Formulae (1) and (2) (described below) which are useful as antagonists of the corticotropin releasing factor.

5 The compounds of the present invention exhibit activity as corticotropin releasing factor antagonists and appear to suppress CRF hypersecretion. The present invention also includes pharmaceutical compositions containing such compounds

10 of Formulae (1) and (2), and methods of using such compounds for the suppression of CRF hypersecretion, and/or for the treatment of anxiogenic disorders.

According to yet another aspect of the invention, the compounds provided by this invention (and especially labelled compounds of this invention) are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the CRF receptor.

20

DETAILED DESCRIPTION OF INVENTION

[1] The present invention comprises a method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms,

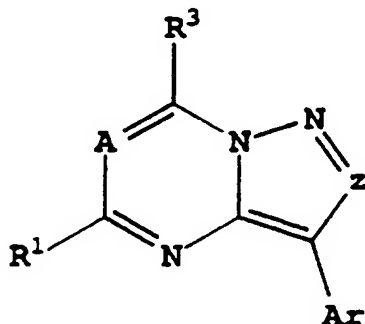
25 inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic

30 lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by

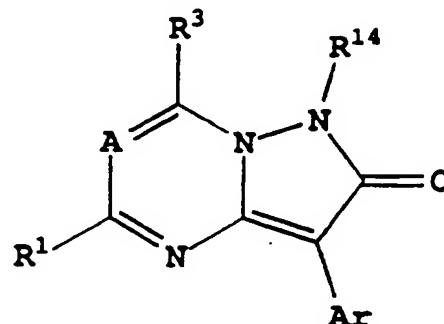
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antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of

5 Formulae (1) or (2):



(1)



(2)

and isomers thereof, stereoisomeric forms thereof, or

10 mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein:

A is N or CR;

15

Z is N or CR²;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-

20 dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R⁴ groups and each Ar is

25 attached to an unsaturated carbon atom;

R is independently selected at each occurrence from
H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,
C₃-C₆ cycloalkyl, C₄-C₇ cycloalkylalkyl, halo,
CN, C₁-C₄ haloalkyl;

5

R¹ is independently selected at each occurrence from
H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,
halo, CN, C₁-C₄ haloalkyl, C₁-C₁₂ hydroxyalkyl,
C₂-C₁₂ alkoxyalkyl, C₂-C₁₀ cyanoalkyl, C₃-C₆
cycloalkyl, C₄-C₁₀ cycloalkylalkyl, NR⁹R¹⁰, C₁-
C₄ alkyl-NR⁹R¹⁰, NR⁹COR¹⁰, OR¹¹, SH or S(O)_nR¹²;

10

R² is selected from H, C₁-C₄ alkyl, C₂-C₄ alkenyl,
C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₀
cycloalkylalkyl, C₁-C₄ hydroxyalkyl, halo, CN,
-NR⁶R⁷, NR⁹COR¹⁰, -NR⁶S(O)_nR⁷, S(O)_nNR⁶R⁷, C₁-
C₄ haloalkyl, -OR⁷, SH or -S(O)_nR¹²;

15

R³ is selected from:

20

-H, OR⁷, SH, S(O)_nR¹³, COR⁷, CO₂R⁷,
OC(O)R¹³, NR⁸COR⁷, N(COR⁷)₂, NR⁸CONR⁶R⁷,
NR⁸CO₂R¹³, NR⁶R⁷, NR^{6a}R^{7a}, N(OR⁷)R⁶,
CONR⁶R⁷, aryl, heteroaryl and heterocyclyl,
or

25

-C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
C₃-C₈ cycloalkyl, C₅-C₈ cycloalkenyl, C₄-
C₁₂ cycloalkylalkyl or C₆-C₁₀
cycloalkenylalkyl, each optionally
substituted with 1 to 3 substituents

30

independently selected at each occurrence
from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo,
C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³,
NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
heteroaryl and heterocyclyl;

35

R^4 is independently selected at each occurrence from:

5 C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, NO₂,
halo, CN, C₁-C₄ haloalkyl, NR⁶R⁷, NR⁸COR⁷,
NR⁸CO₂R⁷, COR⁷, OR⁷, CONR⁶R⁷, CO(NOR⁹)R⁷, CO₂R⁷,
or S(O)_nR⁷, where each such C₁-C₁₀ alkyl, C₂-
C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl
and C₄-C₁₂ cycloalkylalkyl are optionally
10 substituted with 1 to 3 substituents
independently selected at each occurrence from
C₁-C₄ alkyl, NO₂, halo, CN, NR⁶R⁷, NR⁸COR⁷,
NR⁸CO₂R⁷, COR⁷, OR⁷, CONR⁶R⁷, CO₂R⁷, CO(NOR⁹)R⁷,
or S(O)_nR⁷;

15

R^6 and R^7 , R^{6a} and R^{7a} are independently selected at
each occurrence from:

-H,
-C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
20 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
or C₆-C₁₄ cycloalkenylalkyl, each
optionally substituted with 1 to 3
25 substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-
C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
30 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
heteroaryl or heterocyclyl,
-aryl, aryl(C₁-C₄ alkyl), heteroaryl,
heteroaryl(C₁-C₄ alkyl), heterocyclyl or
heterocyclyl(C₁-C₄ alkyl);

35

alternatively, NR^6R^7 and $\text{NR}^{6a}\text{R}^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C₁-C₄ alkyl groups;

5

R^8 is independently selected at each occurrence from H or C₁-C₄ alkyl;

10

R^9 and R^{10} are independently selected at each occurrence from H, C₁-C₄ alkyl, or C₃-C₆ cycloalkyl;

15

R^{11} is selected from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆ cycloalkyl;

R^{12} is C₁-C₄ alkyl or C₁-C₄ haloalkyl;

20

R^{13} is selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-, heteroaryl or heteroaryl(C₁-C₄ alkyl)-;

25

R^{14} is selected from C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₃-C₈ cycloalkyl, or C₄-C₁₂ cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR^{15} , SH, $\text{S(O)}_n\text{R}^{15}$, COR^{15} , CO_2R^{15} , OC(O)R^{15} , $\text{NR}^8\text{COR}^{15}$, $\text{N(COR}^{15})_2$, $\text{NR}^8\text{CONR}^{16}\text{R}^{15}$, $\text{NR}^8\text{CO}_2\text{R}^{15}$, $\text{NR}^{16}\text{R}^{15}$, $\text{CONR}^{16}\text{R}^{15}$, and C₁-C₆ alkylthio, C₁-C₆ alkylsulfinyl and C₁-C₆ alkylsulfonyl;

30

R^{15} and R^{16} are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀

35

cycloalkyl, C₄-C₁₆ cycloalkylalkyl, except that for S(O)_nR¹⁵, R¹⁵ cannot be H;

aryl is phenyl or naphthyl, each optionally
5 substituted with 1 to 5 substituents
independently selected at
each occurrence from C₁-C₆ alkyl, C₃-
C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano,
OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵,
10 NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵,
NR¹⁶R¹⁵, and CONR¹⁶R¹⁵;

heteroaryl is pyridyl, pyrimidinyl, triazinyl,
furanyl, pyranyl, quinolinyl, isoquinolinyl,
15 thienyl, imidazolyl, thiazolyl, indolyl,
pyrrolyl, oxazolyl, benzofuranyl, benzothienyl,
benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-
dihydrobenzothienyl or 2,3-dihydrobenzofuranyl,
each being optionally substituted with 1 to 5
20 substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
S(O)_nR¹⁵, -COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵,
N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, and
25 CONR¹⁶R¹⁵;

heterocyclyl is saturated or partially saturated
heteroaryl, optionally substituted with 1 to 5
substituents independently selected at each
30 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵,
N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁵R¹⁶, and
CONR¹⁶R¹⁵;

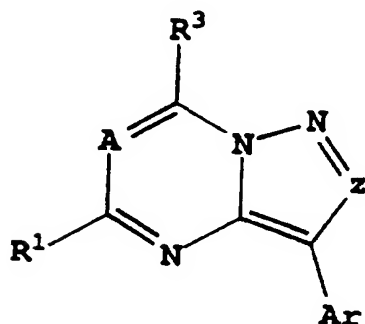
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n is independently at each occurrence 0, 1 or 2,

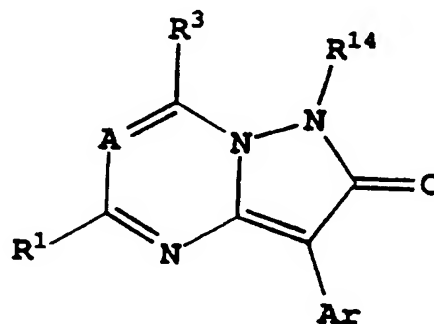
[2] Preferred methods of the present invention are methods in wherein in the compound of Formulae (1) or (2), Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R⁴ substituents.

[3] Further preferred methods of the above invention are methods wherein, in the compound of Formulae (1) or (2), A is N, Z is CR², Ar is 2,4-dichlorophenyl, 2,4-dimethylphenyl or 2,4,6-trimethylphenyl, R¹ and R² are CH₃, and R³ is NR⁶Ar^{7a}.

[4] The present invention comprises compounds of Formulae (1) or (2):



(1)



(2)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein:

A is N or CR;

Z is N or CR²;

Ar is selected from phenyl, naphthyl, pyridyl,
 5 pyrimidinyl, triazinyl, furanyl, thienyl,
 benzothienyl, benzofuranyl, 2,3-
 dihydrobenzofuranyl, 2,3-dihydrobenzothienyl,
 indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-
 benzopyranyl, tetralinyl, each Ar optionally
 10 substituted with 1 to 5 R⁴ groups and each Ar is
 attached to an unsaturated carbon atom;

R is independently selected at each occurrence from
 H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,
 15 C₃-C₆ cycloalkyl, C₄-C₇ cycloalkylalkyl, halo,
 CN, C₁-C₄ haloalkyl;

R¹ is independently selected at each occurrence from
 H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,
 20 halo, CN, C₁-C₄ haloalkyl, C₁-C₁₂ hydroxyalkyl,
 C₂-C₁₂ alkoxyalkyl, C₂-C₁₀ cyanoalkyl, C₃-C₆
 cycloalkyl, C₄-C₁₀ cycloalkylalkyl, NR⁹R¹⁰, C₁-
 C₄ alkyl-NR⁹R¹⁰, NR⁹COR¹⁰, OR¹¹, SH or S(O)_nR¹²;

25 R² is selected from H, C₁-C₄ alkyl, C₂-C₄ alkenyl,
 C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₀
 cycloalkylalkyl, C₁-C₄ hydroxyalkyl, halo, CN,
 -NR⁶R⁷, NR⁹COR¹⁰, -NR⁶S(O)_nR⁷, S(O)_nNR⁶R⁷, C₁-
 C₄ haloalkyl, -OR⁷, SH or -S(O)_nR¹²;

30

R³ is selected from:

-H, OR⁷, SH, S(O)_nR¹³, COR⁷, CO₂R⁷,
 OC(O)R¹³, NR⁸COR⁷, N(COR⁷)₂, NR⁸CONR⁶R⁷,
 NR⁸CO₂R¹³, NR⁶R⁷, NR^{6a}R^{7a}, N(OR⁷)R⁶,
 35 CONR⁶R⁷, aryl, heteroaryl and
 heterocyclyl, or

-C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₈ cycloalkyl, C₅-C₈ cycloalkenyl, C₄-
 C₁₂ cycloalkylalkyl or C₆-C₁₀
 cycloalkenylalkyl, each optionally
 5 substituted with 1 to 3 substituents
 independently selected at each occurrence
 from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo,
 C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³,
 10 NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl and heterocyclyl;

R⁴ is independently selected at each occurrence from:
 15 C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, NO₂,
 halo, CN, C₁-C₄ haloalkyl, NR⁶R⁷, NR⁸COR⁷,
 NR⁸CO₂R⁷, COR⁷, OR⁷, CONR⁶R⁷, CO(NOR⁹)R⁷, CO₂R⁷,
 or S(O)_nR⁷, where each such C₁-C₁₀ alkyl, C₂-
 20 C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl
 and C₄-C₁₂ cycloalkylalkyl are optionally
 substituted with 1 to 3 substituents
 independently selected at each occurrence from
 C₁-C₄ alkyl, NO₂, halo, CN, NR⁶R⁷, NR⁸COR⁷,
 25 NR⁸CO₂R⁷, COR⁷ OR⁷, CONR⁶R⁷, CO₂R⁷, CO(NOR⁹)R⁷,
 or S(O)_nR⁷;

R⁶ and R⁷, R^{6a} and R^{7a} are independently selected at
 each occurrence from:
 30 -H,
 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 35 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3

- substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl, -aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄ alkyl), alternatively, NR⁶R⁷ and NR^{6a}R^{7a} are independently piperidine, pyrrolidine, piperazine; N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C₁-C₄ alkyl groups;
- R⁸ is independently selected at each occurrence from H or C₁-C₄ alkyl;
- R⁹ and R¹⁰ are independently selected at each occurrence from H, C₁-C₄ alkyl, or C₃-C₆ cycloalkyl;
- R¹¹ is selected from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆ cycloalkyl;
- R¹² is C₁-C₄ alkyl or C₁-C₄ haloalkyl;
- R¹³ is selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-, heteroaryl or heteroaryl(C₁-C₄ alkyl)-;
- R¹⁴ is selected from C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₃-C₈ cycloalkyl, or C₄-C₁₂ cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected

at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, and C₁-C₆ alkylthio, C₁-C₆ alkylsulfinyl and C₁-C₆ alkylsulfonyl;

R¹⁵ and R¹⁶ are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₄-C₁₆ cycloalkylalkyl, except that for S(O)_nR¹⁵, R¹⁵ cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, and CONR¹⁶R¹⁵;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, -COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, and CONR¹⁶R¹⁵;

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁵R¹⁶, and CONR¹⁶R¹⁵;

n is independently at each occurrence 0, 1 or 2,

with the provisos that:

- (1) when A is N, Z is CR², R² is H, R³ is -OR⁷ or -OCOR¹³, and R⁷ is H, then R¹ is not H, OH or SH;
- (2) when A is N, Z is CR², R¹ is CH₃ or C₂H₅, R² is H, and R³ is OH, H, CH₃, C₂H₅, C₆H₅, n-C₃H₇, i-C₃H₇, SH, SCH₃, NHC₄H₉, or N(C₂H₅)₂, then Ar is not phenyl or m-CH₃-phenyl;
- (3) when A is N, Z is CR², R² is H, and Ar is pyridyl, pyrimidinyl or pyrazinyl, and R³ is NR^{6a}R^{7a}, then R^{6a} and R^{7a} are not H or alkyl;
- (4) when A is N, Z is CR², and R² is SO₂NR⁶R⁷, then R³ is not OH or SH;
- (5) when A is CR and Z is CR², then R² is not -NR⁶SO₂R⁷ or -SO₂NR⁶R⁷;
- (6) when A is N, Z is CR² and R² is -NR⁶SO₂R⁷ or -SO₂NR⁶R⁷, then R³ is not OH or SH;
- (7) when A is N, Z is CR², R¹ is methyl or ethyl, R² is H, and R³ is H, OH, CH₃, C₂H₅, C₆H₅, n-C₃H₇,

iso-C₃H₇, SH, SCH₃, NH(n-C₄H₉), or N(C₂H₅)₂, then Ar is not unsubstituted phenyl or m-methylphenyl;

- 5 (8) when A is CR, Z is CR², R² is H, phenyl or alkyl, R³ is NR⁸COR⁷ and Ar is phenyl or phenyl substituted with phenylthio, then R⁷ is not aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄ alkyl);
- 10 (9) when A is CR, Z is CR², R² is H or alkyl, Ar is phenyl, and R³ is SR¹³ or NR^{6a}R^{7a}, then R¹³ is not aryl or heteroaryl and R^{6a} and R^{7a} are not H or aryl; or
- 15 (10) when A is CH, Z is CR², R¹ is OR¹¹, R² is H, R³ is OR⁷, and R⁷ and R¹¹ are both H, then Ar is not phenyl, p-Br-phenyl, p-Cl-phenyl, p-NHCOCH₃-phenyl, p-CH₃-phenyl, pyridyl or naphthyl;
- 20 (11) when A is CH, Z is CR², R² is H, Ar is unsubstituted phenyl, and R³ is CH₃, C₂H₅, CF₃ or C₆H₄F, then R₁ is not CF₃ or C₂F₅;
- 25 (12) when A is CR, R is H, Z is CR², R² is OH, and R¹ and R³ are H, then Ar is not phenyl;
- (13) when A is CR, R is H, Z is CR², R² is OH or NH₂, R¹ and R³ are CH₃, then Ar is not 4-phenyl-3-cyano-2-aminopyrid-2-yl.

- 30 [5] Preferred compounds of the above invention are compounds of Formulae (1) and (2) and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof with the additional provisos that: (1) when A is N, R¹ is H, C₁-C₄ alkyl, halo, CN, C₁-C₁₂ hydroxyalkyl, C₁-C₄
- 35

alkoxyalkyl or $\text{SO}_2(\text{C}_1\text{-C}_4 \text{ alkyl})$, R^3 is $\text{NR}^{6a}\text{R}^{7a}$ and R^{6a} is unsubstituted $\text{C}_1\text{-C}_4$ alkyl, then R^{7a} is not phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl,
5 benzothiazolyl, indolyl or $\text{C}_3\text{-C}_6$ cycloalkyl; and (2) A is N, R^1 is H, $\text{C}_1\text{-C}_4$ alkyl, halo, CN, $\text{C}_1\text{-C}_{12}$ hydroxyalkyl, $\text{C}_1\text{-C}_4$ alkoxyalkyl or $\text{SO}_2(\text{C}_1\text{-C}_4 \text{ alkyl})$, R^3 is $\text{NR}^{6a}\text{R}^{7a}$ and R^{7a} is unsubstituted $\text{C}_1\text{-C}_4$ alkyl, then R^{6a} is not phenyl, naphthyl, thienyl,
10 benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, indolyl or $\text{C}_3\text{-C}_6$ cycloalkyl.

[6] Preferred compounds of the above invention also
15 include compounds of Formulae (1) and (2) and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each
20 optionally substituted with 1 to 4 R^4 substituents.

[7]. Preferred compounds of the above invention also include compounds of Formulae (1) and (2) and isomers thereof, stereoisomeric forms thereof, or mixtures of
25 stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is N, Z is CR^2 , Ar is 2,4-dichlorophenyl, 2,4-dimethylphenyl or 2,4,6-trimethylphenyl, R^1 and R^2 are CH_3 , and R^3 is $\text{NR}^{6a}\text{R}^{7a}$.

30
[11] More preferred compounds of the above invention are compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms
35 thereof wherein A is N.

[12] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[13] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R⁴ substituents.

[14] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R³ is NR^{6a}R^{7a} or OR⁷.

[15] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R⁴ substituents, and R³ is NR^{6a}R^{7a} or OR⁷.

[16] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Z is CR².

[17] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of
5 stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R⁴ substituents.

10 [18] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R³ is
15 NR^{6a}R^{7a} or OR⁷.

[19] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of
20 stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

-H,
-C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
25 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl, or C₆-C₁₄ cycloalkenylalkyl, each
optionally substituted with 1 to 3
30 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
35 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C₁-C₄ alkyl)-, heteroaryl, heteroaryl(C₁-C₄ alkyl)-, heterocyclyl or heterocyclyl(C₁-C₄ alkyl)-; and

R^{7a} is independently selected at each occurrence from:

- 5 -H,
 -C₅-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
10 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-
15 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
20 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 heterocyclyl(C₁-C₄ alkyl);

alternatively, NR⁶R⁷ and NR^{6a}R^{7a} are independently
piperidine, pyrrolidine, piperazine, N-
25 methylpiperazine, morpholine or thiomorpholine, each
 optionally substituted with 1-3 C₁-C₄ alkyl groups.

[20] More preferred compounds of the above invention
also include compounds and isomers thereof,
30 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein R^{6a}
 and R^{7a} are identical and are selected from:
35 -C₁-C₄ alkyl or C₃-C₆ cycloalkyl, each optionally
 substituted with 1 to 3 substituents
 independently selected at each occurrence from

C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, -COR¹⁵,
CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
5 aryl, heteroaryl or heterocyclyl, and
-aryl or heteroaryl.

[21] More preferred compounds of the above invention
also include compounds and isomers thereof,
10 stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein
R^{6a} is selected from:

-H,
15 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
or C₆-C₁₄ cycloalkenylalkyl, each
20 optionally substituted with 1 to 3
substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-
C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
25 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
heteroaryl or heterocyclyl,
-aryl, aryl(C₁-C₄ alkyl), heteroaryl,
heteroaryl(C₁-C₄ alkyl), heterocyclyl or
30 heterocyclyl(C₁-C₄ alkyl);

R^{7a} is selected from:

-C₁-C₄ alkyl and each such C₁-C₄ alkyl is
substituted with 1-3 substituents
independently selected at each occurrence from
35 C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,

CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
aryl, heteroaryl or heterocyclyl.

- 5 [22] More preferred compounds of the above invention
also include compounds and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein
10 one of R^{6a} and R^{7a} is selected from:
-C₃-C₆ cycloalkyl, each such C₃-C₆ cycloalkyl
optionally substituted with 1-3 substituents
independently selected at each occurrence from
C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
15 haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,
CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
aryl, heteroaryl or heterocyclyl,
-aryl,
20 -heteroaryl or
-heterocyclyl,
and the other of R^{6a} and R^{7a} is unsubstituted C₁-C₄
alkyl.
- 25 [23] More preferred compounds of the above invention
also include compounds and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein
30 R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl,
each such C₁-C₁₀ alkyl optionally substituted with
1 to 3 substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³,
35 COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,

$R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[24] More preferred compounds of the above invention
5 also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar
10 is optionally substituted with 1 to 4 R^4 substituents, and R^3 is NR^6aR^7a or OR^7 .

[25] More preferred compounds of the above invention also include compounds and isomers thereof,
15 stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

-H,
20 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl, or C₆-C₁₄ cycloalkenylalkyl, each
25 optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR^{15} , SH, $S(O)_nR^{13}$, COR^{15} , CO_2R^{15} ,
30 $OC(O)R^{13}$, NR^8COR^{15} , $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,
-aryl, aryl(C₁-C₄ alkyl)-, heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or
35 heterocyclyl(C₁-C₄ alkyl);

R^{7a} is independently selected at each occurrence from:

- H,
- C₅-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 5 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3
 substituents independently selected at each
 10 occurrence from C₁-C₆ alkyl, C₃-
 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 15 heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 heterocyclyl(C₁-C₄ alkyl),
- 20 alternatively, NR⁶R⁷ and NR^{6a}R^{7a} are independently
 piperidine, pyrrolidine, piperazine, N-
 methylpiperazine, morpholine or thiomorpholine, each
 optionally substituted with 1-3 C₁-C₄ alkyl groups.
- 25 [26] More preferred compounds of the above invention
 also include compounds and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein R^{6a}
 30 and R^{7a} are identical and are selected from:
 -C₁-C₄ alkyl or C₃-C₆ cycloalkyl, each optionally
 substituted with 1 to 3 substituents
 independently selected at each occurrence from
 C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
 35 haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, -COR¹⁵,

CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
aryl, heteroaryl or heterocyclyl, and
-aryl or heteroaryl.

5

[27] More preferred compounds of the above invention
also include compounds and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
10 acceptable salt or pro-drug forms thereof wherein R^{6a}
and R^{7a} are identical and are

-C₁-C₄ alkyl, each such C₁-C₄ alkyl
optionally substituted with 1 to 3
substituents independently selected at each
15 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
S(O)_nR¹³, -COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵,
N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵,
CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

20

[28] More preferred compounds of the above invention
also include compounds and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
25 acceptable salt or pro-drug forms thereof wherein
R^{6a} is selected from:

-H,
-C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
30 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
or C₆-C₁₄ cycloalkenylalkyl, each
optionally substituted with 1 to 3
substituents independently selected at each
35 occurrence from C₁-C₆ alkyl, C₃-
C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,

cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
heteroaryl or heterocyclyl,
5 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
heteroaryl(C₁-C₄ alkyl), heterocyclyl or
heterocyclyl(C₁-C₄ alkyl);

R^{7a} is:

-C₁-C₄ alkyl and each such C₁-C₄ alkyl is
10 substituted with 1-3 substituents
independently selected at each occurrence from
C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,
CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
15 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
aryl, heteroaryl or heterocyclyl.

[29] More preferred compounds of the above invention
also include compounds and isomers thereof,
20 stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein one of
R^{6a} and R^{7a} is selected from:

-C₃-C₆ cycloalkyl, each such C₃-C₆ cycloalkyl
25 optionally substituted with 1-3 substituents
independently selected at each occurrence from
C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,
CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
30 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
aryl, heteroaryl or heterocyclyl,
-aryl,
-heteroaryl or
-heterocyclyl,

35 and the other of R^{6a} and R^{7a} is unsubstituted C₁-C₄
alkyl.

[30] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl, each such C₁-C₁₀ alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

[31] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein

- Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R⁴ substituents,
- R³ is NR^{6a}R^{7a} or OR⁷ and
- R¹ and R² are independently selected from H, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₄-C₁₀ cycloalkylalkyl.

[32] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

-H,

- 5 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-
 10 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
 15 -aryl, aryl(C₁-C₄ alkyl)-, heteroaryl, heteroaryl(C₁-
 C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄
 alkyl);
 R^{7a} is independently selected at each occurrence from:
 -H,
 20 -C₅-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3
 25 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-
 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 30 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 heterocyclyl(C₁-C₄ alkyl),
 35

alternatively, NR^{6R^7} and NR^{6aR^7a} are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1 - C_4 alkyl groups.

5

[33] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:

- C_1 - C_4 alkyl or C_3 - C_6 cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo, C_1 - C_4 haloalkyl, cyano, OR^{15} , SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15} , $OC(O)R^{13}$, NR^8COR^{15} , $N(COR^{15})_2$, $NR^8CONR^{16R^{15}}$, $NR^8CO_2R^{13}$, $NR^{16R^{15}}$, $CONR^{16R^{15}}$, aryl, heteroaryl or heterocyclyl, and
-aryl or heteroaryl.

15

20

[34] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are

- C_1 - C_4 alkyl, each such C_1 - C_4 alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo, C_1 - C_4 haloalkyl, cyano, OR^{15} , SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15} , $OC(O)R^{13}$, NR^8COR^{15} , $N(COR^{15})_2$, $NR^8CONR^{16R^{15}}$, $NR^8CO_2R^{13}$, $NR^{16R^{15}}$, $CONR^{16R^{15}}$, aryl, heteroaryl or heterocyclyl.

30

35

[35] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is selected from:

- H,
 - C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl, or C₆-C₁₄ cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl;
 - aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄ alkyl);
- R^{7a} is:
- C₁-C₄ alkyl and each such C₁-C₄ alkyl is substituted with 1-3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

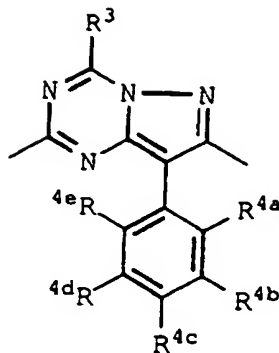
[36] More preferred compounds of the above invention also include compounds and isomers thereof,

stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein one of R^{6a} and R^{7a} is selected from:

- 5 -C₃-C₆ cycloalkyl, each such C₃-C₆ cycloalkyl
 optionally substituted with 1-3 substituents
 independently selected at each occurrence from
 C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
 haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,
10 CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
 aryl, heteroaryl or heterocyclyl,
 -aryl,
 -heteroaryl or
15 -heterocyclyl,
and the other of R^{6a} and R^{7a} is unsubstituted C₁-C₄
alkyl.

- [37] More preferred compounds of the above invention
20 also include compounds and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein
 R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl,
25 each such C₁-C₁₀ alkyl optionally substituted with
 1 to 3 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
 halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³,
 COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
30 R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl.

- [38] Specifically preferred compounds of the above
invention are compounds of Formula (50)
35



FORMULA (50)

- 5 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, selected from the group consisting of:
- 10 a compound of Formula (50) wherein R³ is -NHCH(n-Pr)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R³ is -N(Et)(n-Bu), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R³ is -(n-Pr)(CH₂CPr), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R³ is -N(CH₂CH₂OMe)₂, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R³ is -NHCH(Et)(n-Bu), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R³ is -NHCH(Et)(CH₂OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OEt)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-N(Me)(Ph)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(n-Pr)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(n-Pr)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-OEt$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 45

- a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-N(CH_2CN)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-NHCH(Me)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-OCH(Et)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-N(n-Pr)(CH_2cPr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $-NHCH(Me)(CH_2N(Me)_2)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(cPr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is $-N(n-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $-N(n-Bu)(CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 40 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 45

- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OEt)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 15 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2CH_2OMe)(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 20 a compound of Formula (50) wherein R^3 is morpholino, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NH(c-Pr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is CN, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 45 a compound of Formula (50) wherein R^3 is $-NCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

- 5 a compound of Formula (50) wherein R³ is
-NHCH(CH₂OMe)(CH₂CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c}
is Br, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R³ is -NHCH(CH₂OMe)₂,
R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e}
is H;
- 15 a compound of Formula (50) wherein R³ is -N(CH₂CH₂OMe)₂,
R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e}
is H;
- 20 a compound of Formula (50) wherein R³ is -NHCH(Et)₂, R^{4a}
is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is
H;
- 25 a compound of Formula (50) wherein a compound of Formula
(50) wherein R³ is -N(Et)₂, R^{4a} is Me, R^{4b} is H,
R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- 30 a compound of Formula (50) wherein R³ is -NHCH(CH₂OMe)₂,
R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is
H;
- 35 a compound of Formula (50) wherein R³ is
-NHCH(CH₂OMe)(CH₂CH₂OMe), R^{4a} is Cl, R^{4b} is H, R^{4c}
is Me, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R³ is -N(c-
Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d}
is Me and R^{4e} is H;
- 45 a compound of Formula (50) wherein R³ is -N(c-
Pr)(CH₂CH₂CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d}
is H and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is (S)-
 $\text{NHCH}(\text{CH}_2\text{OMe})(\text{CH}_2\text{CH}_2\text{OMe})$, R^{4a} is Cl, R^{4b} is H, R^{4c}
 is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is
 $-\text{NHCH}(\text{CH}_2\text{OMe})(\text{CH}_2\text{CH}_2\text{OMe})$, R^{4a} is Cl, R^{4b} is H, R^{4c}
 is Cl, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-\text{NHCH}(\text{Et})_2$, R^{4a}
 is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-\text{N}(\text{CH}_2\text{CH}_2\text{OMe})_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is
 H;
- 15 a compound of Formula (50) wherein R^3 is
 $-\text{NH}(\text{CH}_2\text{OMe})(\text{CH}_2\text{-iPr})$, R^{4a} is Me, R^{4b} is H, R^{4c} is
 Me, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $-\text{N}(\text{CH}_2\text{CH}_2\text{OMe})_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is H, R^{4d} is H and R^{4e} is
 H;
- 25 a compound of Formula (50) wherein R^3 is $-\text{N}(\text{CH}_2\text{CH}_2\text{OMe})_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is NMe_2 , R^{4d} is H and R^{4e}
 is H;
- a compound of Formula (50) wherein R^3 is
 $-\text{NHCH}(\text{CH}_2\text{OMe})(\text{n-Pr})$, R^{4a} is Me, R^{4b} is H, R^{4c} is
 30 Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is
 $-\text{NHCH}(\text{CH}_2\text{OEt})(\text{Et})$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me,
 R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is
 $-\text{NHCH}(\text{CH}_2\text{OMe})(\text{CH}_2\text{CH}_2\text{OMe})$, R^{4a} is Me, R^{4b} is H, R^{4c}
 is NMe_2 , R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-\text{N}(\text{Et})_2$, R^{4a} is
 Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-\text{NHCH}(\text{Et})_2$, R^{4a}
 is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 45

- a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe₂, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is (S)-
 $NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is
 $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is (S)-
 $NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is
 $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (50) wherein R^3 is $-NH(Et)(CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)(CH_2CH_2OH)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is CN, R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OH)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H; and
- 5 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H.
- 10 [39] More specifically preferred is 4-(bis-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and
- 15 pharmaceutically acceptable salt or pro-drug forms thereof.
- [40] More specifically preferred is 4-(bis-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2,5-dimethyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine and
- 20 isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.
- 25 [41] More preferred are compounds of the above invention are compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms
- 30 thereof wherein A is CR.
- [42] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of
- 35 stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[43] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

[44] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is NR^6aR^7a or OR^7 .

[45] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is NR^6aR^7a or OR^7 .

[46] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Z is CR^2 .

[47] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is

phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R⁴ substituents.

5 [48] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R³ is NR^{6a}R^{7a} or OR⁷.

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[49] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is 15 phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R⁴ substituents, and R³ is NR^{6a}R^{7a} or OR⁷.

20 [50] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein 25 R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl, and each such C₁-C₁₀ alkyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, 30 SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

[51] More preferred compounds of the above invention 35 also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of

stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein

-Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R⁴ substituents,

-R³ is NR^{6a}R^{7a} or OR⁷ and

-R¹ and R² are independently selected from H, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₄-C₁₀ cycloalkylalkyl.

10

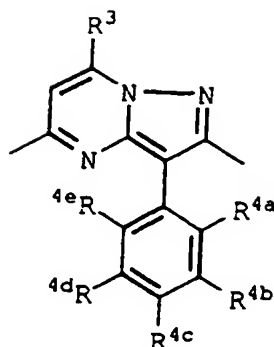
[52] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl, and each such C₁-C₁₀ alkyl is optionally

15

substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

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25 [53] Specifically preferred compounds of the above invention are compounds of Formula (51)



FORMULA (51)

- 5 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof selected from the group consisting of:
- 10 a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

- a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (51) wherein R^3 is $-N(n-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(n-Bu)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) wherein R^3 is (S) $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (51) wherein R^3 is $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (51) wherein R^3 is $-NH(Et)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

- a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (51) wherein R^3 is (S) $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (51) wherein R^3 is $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is $-N(n-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) wherein R^3 is (S) $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (51) wherein R^3 is $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (51) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

- a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
5
- a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
25
- a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
30
- a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is $-N(Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(Bu)(Et)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
40
- a compound of Formula (51) wherein R^3 is $-NHCH(Et)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
45

- a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NEt_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 15 and
- a compound of Formula (51) wherein R^3 is $-N(Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H.
- 20

[54] More specifically preferred is 7-(3-pentylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

25

[55] More specifically preferred is 7-(Diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

30

35

[56] More specifically preferred is 7-(N-(3-cyanopropyl)-N-propylamino)-2,5-dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimidine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and

40

pharmaceutically acceptable salt or pro-drug forms thereof.

The present invention also provides
5 pharmaceutical compositions comprising compounds of Formulae (1) and (2) and a pharmaceutically acceptable carrier.

Many compounds of this invention have one or more
10 asymmetric centers or planes. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all
15 such stable isomers are contemplated in the present invention. The compounds may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from
20 optically active starting materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

25 The term "alkyl" includes both branched and straight-chain alkyl having the specified number of carbon atoms. Commonly used abbreviations have the following meanings: Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl. The prefix "n" means a straight
30 chain alkyl. The prefix "c" means a cycloalkyl. The prefix "(S)" means the S enantiomer and the prefix "(R)" means the R enantiomer. Alkenyl" includes hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-
35 carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the

like. "Alkynyl" includes hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like. "Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms, substituted with 1 or more halogen; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-, bi- or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and so forth. "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

The term "substituted", as used herein, means that one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "appropriate amino acid protecting group" means any group known in the art of organic synthesis for the protection of amine or carboxylic acid groups. Such amine protecting groups include those listed in Greene and Wuts, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1991) and "The Peptides: Analysis, Synthesis,

Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Any amine protecting group known in the art can be used. Examples of amine protecting groups include, but are not limited to, the following: 1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; 2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate types such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; 5) alkyl types such as triphenylmethyl and benzyl; 6) trialkylsilane such as trimethylsilane; and 7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl.

The term "pharmaceutically acceptable salts" includes acid or base salts of the compounds of Formulae (1) and (2). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing

Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

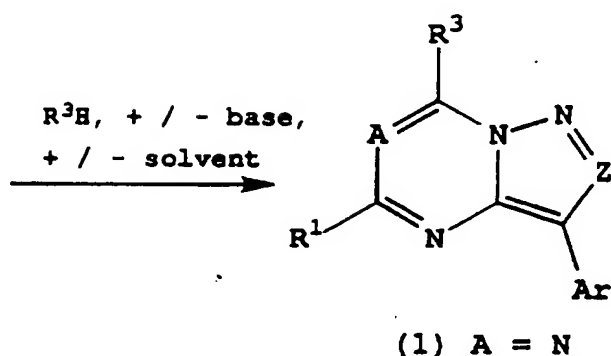
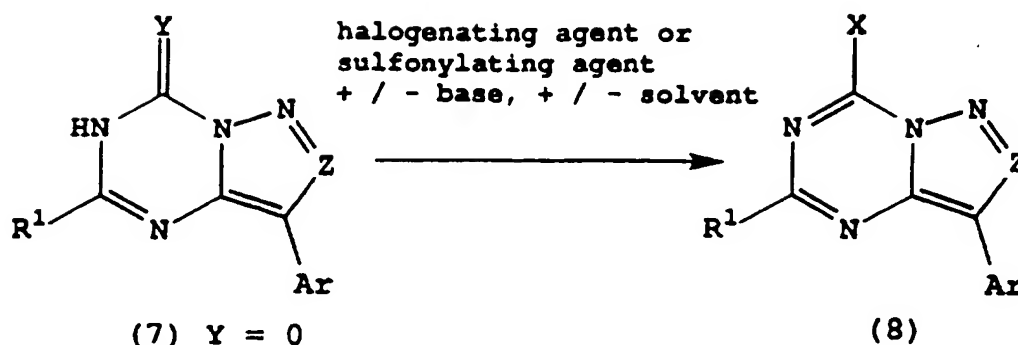
"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula (I) or (II) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of formula (I) and (II) are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formulas (I) and (II); and the like.

The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize abnormal level of CRF or treat the symptoms of affective disorder, anxiety or depression in a host.

Syntheses

Some compounds of Formula (1) may be prepared from intermediate compounds of Formula (7), using the procedures outlined in Scheme 1:

SCHEME 1



- Compounds of Formula (7) (where Y is O) may be treated with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to give products of Formula (8) (where X is halogen, alkanesulfonyloxy, arylsulfonyloxy or haloalkane-sulfonyloxy). Halogenating agents include, but are not limited to, SOCl_2 , POCl_3 , PCl_3 , PCl_5 , POBr_3 , PBr_3 or PBr_5 . Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (such as methanesulfonyl chloride or methanesulfonic acid anhydride), arylsulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride) or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, alkali metal

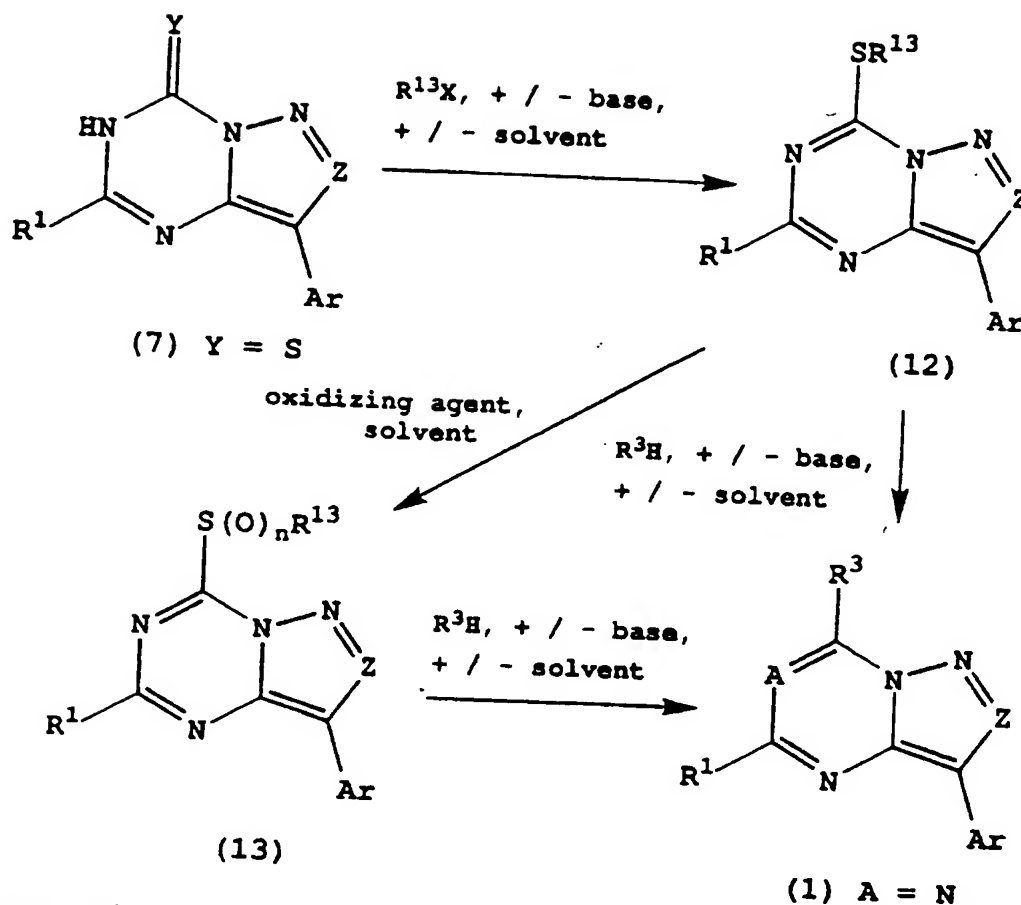
- hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to,
- lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane).
- Preferred reaction temperatures range from -20°C to 100°C.

- Compounds of Formula (8) may be reacted with compounds of Formula R^3H (where R^3 is defined as above except R^3 is not SH, COR^7 , CO_2R^7 , aryl or heteroaryl) in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80 to 250°C to generate compounds of Formula (1). Bases may include, but are not limited to,
- alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably

N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1
5 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides
10 (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range
15 from 0°C to 140°C.

Scheme 2 delineates the procedures for converting intermediate compounds of Formula (7) (where Y is S) to some compounds of Formula (1).

SCHEME 2



Compounds of Formula (7) (where Y is S) may be treated with an alkylating agent R¹³X (where R¹³ is defined as above, except R¹³ is not aryl or heteroaryl) in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium

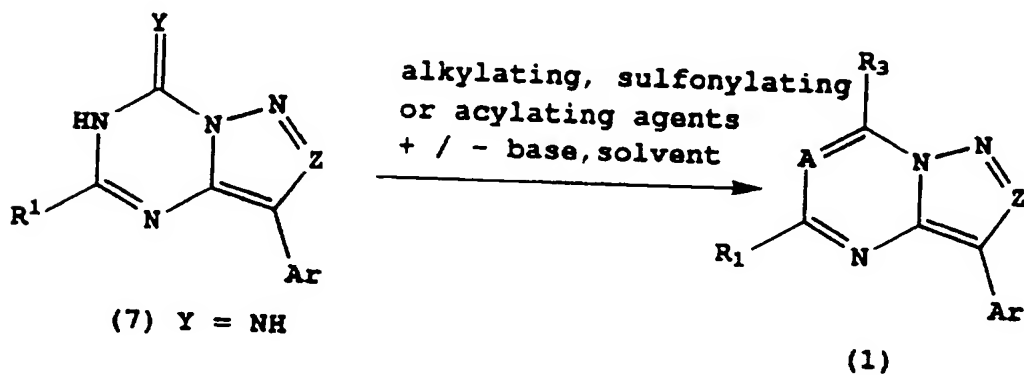
bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -80°C to 100°C.

Compounds of Formula (12) (Formula (1) where R^3 is SR^{13}) may then be reacted with compounds of Formula R^3H to give compounds of Formula (1), using the same conditions and reagents as were used for the conversion of compounds of Formula (8) to compounds of Formula (1) as outlined for Scheme 1 above. Alternatively, compounds of Formula (12) (Formula (1) where R^3 is SR^{13}) may be oxidized to compounds of Formula (13) (Formula (1) where R^3 is $S(O)_nR^{13}$, n is 1,2) by treatment with an oxidizing agent in the presence of an inert solvent at temperatures ranging from -80°C to 250°C. Oxidizing agents include, but are not limited to, hydrogen peroxide, alkane or aryl peracids (preferably peracetic acid or m-chloro-perbenzoic acid), dioxirane, oxone, or sodium periodate. Inert solvents may include, but are not limited to, alkanones (3 to 10 carbons, preferably acetone), water, alkyl alcohols (1 to 6 carbons), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens

(preferably dichloromethane) or combinations thereof. The choices of oxidant and solvent are known to those skilled in the art (cf. Uemura, S., Oxidation of Sulfur, Selenium and Tellurium, in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 7, 762-769). Preferred reaction temperatures range from -20°C to 100°C. Compounds of Formula (13) (Formula (1) where R^3 is $S(O)_nR^{13}$, n is 1,2) may then be reacted with compounds of Formula R^3H to give compounds of Formula (1), using the same conditions and reagents as were used for the conversion of compounds of Formula (8) to compounds of Formula (1) as outlined for Scheme (1) above.

Compounds of Formula (1), where R^3 may be $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-NR^8SO_2R^7$, may be prepared from compounds of Formula (7), where Y is NH, by the procedures depicted in Scheme 3.

SCHEME 3.



$A = N$;
 $R_3 = NR^6R^7, NR^8COR^7,$
 $N(COR^7)_2, NR^8CONR^6R^7,$
 $NR^8CO_2R^{13}$

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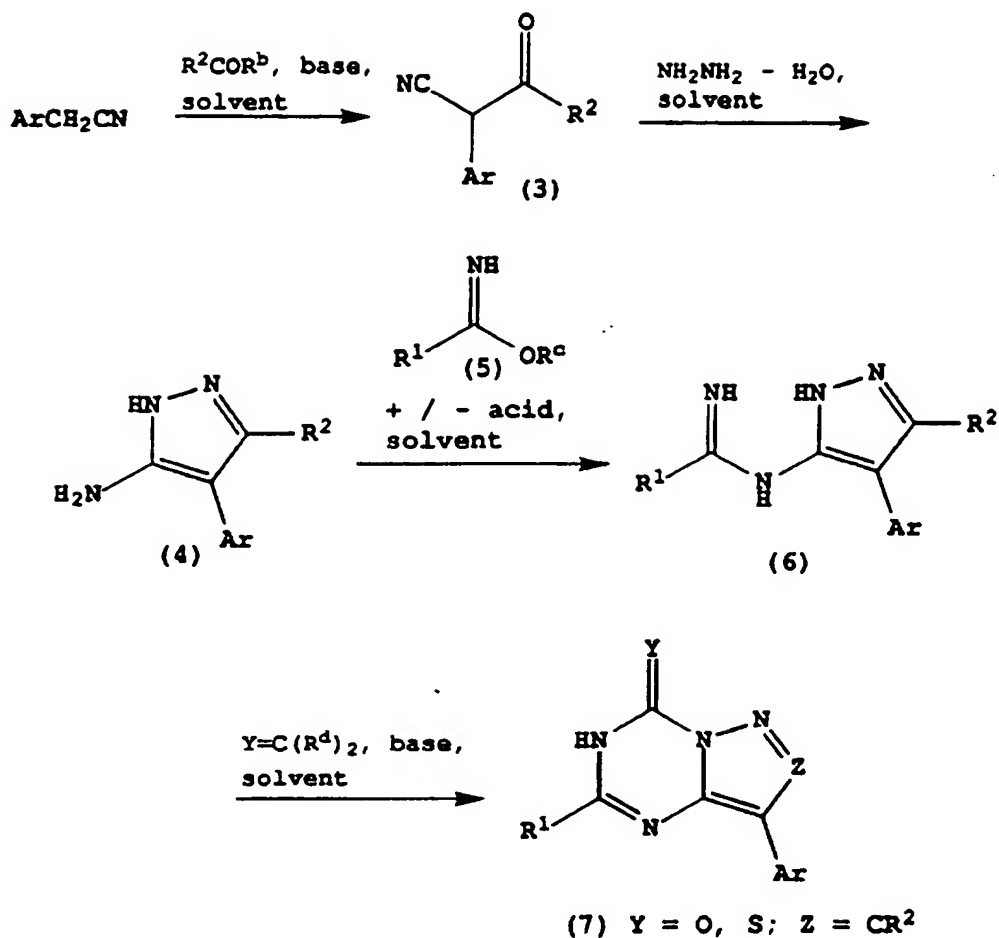
Reaction of compounds of Formula (7), where Y is NH, with alkylating agents, sulfonylating agents or acylating agents or sequential reactions with

combinations thereof, in the presence or absence of a base in an inert solvent at reaction temperatures ranging from -80°C to 250°C may afford compounds of Formula (1), where R³ may be -NR⁸COR⁷, -N(COR⁷)₂,
5 -NR⁸CONR⁶R⁷, -NR⁸CO₂R¹³, -NR⁶R⁷, -NR⁸SO₂R⁷. Alkylating agents may include, but are not limited to, C₁-C₁₀ alkyl-halides, -tosylates, -mesylates or -triflates; C₁-C₁₀ haloalkyl(1 - 10 halogens)-halides, -tosylates, -mesylates or -triflates; C₂-C₈ alkoxyalkyl-halides,
10 -tosylates, -mesylates or -triflates; C₃-C₆ cycloalkyl-halides, -tosylates, -mesylates or -triflates; C₄-C₁₂ cycloalkylalkyl-halides, -tosylates, -mesylates or -triflates; aryl(C₁-C₄ alkyl)-halides, -tosylates, -mesylates or -triflates; heteroaryl(C₁-C₄ alkyl)-
15 halides, -tosylates, -mesylates or -triflates; or heterocyclyl(C₁-C₄ alkyl)-halides, -tosylates, -mesylates or -triflates. Acylating agents may include, but are not limited to, C₁-C₁₀ alkanoyl halides or anhydrides, C₁-C₁₀ haloalkanoyl halides or anhydrides
20 with 1 - 10 halogens, C₂-C₈ alkoxyalkanoyl halides or anhydrides, C₃-C₆ cycloalkanoyl halides or anhydrides, C₄-C₁₂ cycloalkylalkanoyl halides or anhydrides, aroyl halides or anhydrides, aryl(C₁-C₄) alkanoyl halides or anhydrides, heteroaroyl halides or anhydrides,
25 heteroaryl(C₁-C₄) alkanoyl halides or anhydrides, heterocyclylcarboxylic acid halides or anhydrides or heterocyclyl(C₁-C₄) alkanoyl halides or anhydrides. Sulfonylating agents include, but are not limited to, C₁-C₁₀ alkylsulfonyl halides or anhydrides, C₁-C₁₀
30 haloalkylsulfonyl halides or anhydrides with 1 - 10 halogens, C₂-C₈ alkoxyalkylsulfonyl halides or anhydrides, C₃-C₆ cycloalkylsulfonyl halides or anhydrides, C₄-C₁₂ cycloalkylalkylsulfonyl halides or anhydrides, arylsulfonyl halides or anhydrides, aryl(C₁-
35 C₄ alkyl)-, heteroarylsulfonyl halides or anhydrides, heteroaryl(C₁-C₄ alkyl)sulfonyl halides or anhydrides,

heterocyclylsulfonyl halides or anhydrides or heterocyclyl(C₁-C₄ alkyl)sulfonyl halides or anhydrides. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

Scheme 4 delineates procedures, which may be employed to prepare intermediate compounds of Formula (7), where Y is O, S and Z is CR².

SCHEME 4



Compounds of the formula ArCH_2CN are reacted with compounds of the formula R^2COR^b , where R^2 is defined above and R^b is halogen, cyano, lower alkoxy (1 to 6 carbons) or lower alkanoyloxy (1 to 6 carbons), in the presence of a base in an inert solvent at reaction temperatures ranging from -78°C to 200°C to afford compounds of Formula (3). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal

dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

Compounds of Formula (3) may be treated with hydrazine-hydrate in the presence of an inert solvent at temperatures ranging from 0°C to 200°C, preferably 70°C to 150°C, to produce compounds of Formula (4). Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Compounds of Formula (4) may be reacted with compounds of Formula (5) (where R^c is alkyl (1-6 carbons)) in the presence or absence of an acid in the presence of an inert solvent at temperatures ranging from 0°C to 200°C to produce compounds of Formula (6). Acids may include, but are

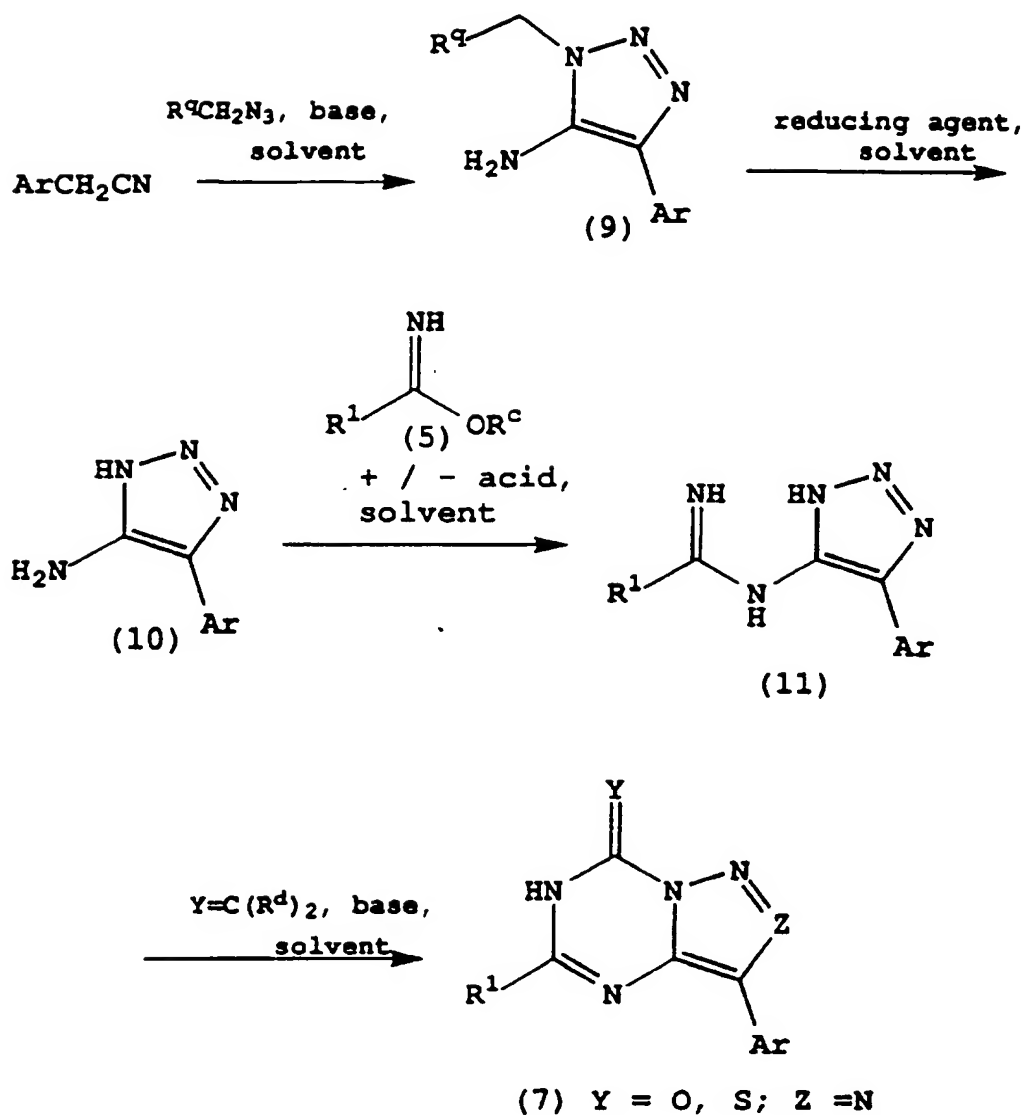
not limited to alkanolic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Inert solvents may include, but are not limited to, water, alkanenitriles (1 to 6 carbons, preferably acetonitrile), halocarbons of 1 to 6 carbons and 1 to 6 halogens (preferably dichloromethane or chloroform), alkyl alcohols of 1 to 10 carbons (preferably ethanol), dialkyl ethers (4 to 12 carbons, preferably diethyl ether or di-isopropylether) or cyclic ethers such as dioxan or tetrahydrofuran. Preferred temperatures range from ambient temperature to 100°C.

Compounds of Formula (6) may be converted to intermediate compounds of Formula (7) by treatment with compounds $C=Y(R^d)_2$ (where Y is O or S and R^d is halogen (preferably chlorine), alkoxy (1 to 4 carbons) or alkylthio (1 to 4 carbons)) in the presence or absence of a base in an inert solvent at reaction temperatures from -50°C to 200°C. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkali metal carbonates, alkali metal hydroxides, trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably

dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred temperatures are 0°C to 150°C.

Intermediate compounds of Formula (7), where Z is N, may be synthesized according the methods outlined in Scheme 5.

SCHEME 5



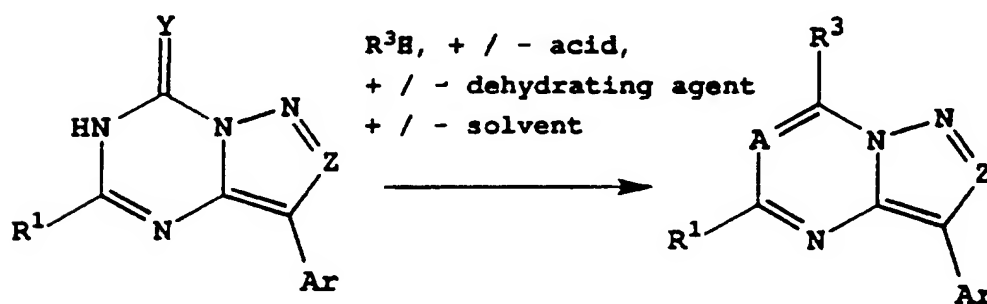
Compounds of ArCH_2CN are reacted with compounds of Formula $\text{R}^9\text{CH}_2\text{N}_3$ (where R^9 is a phenyl group optionally substituted by H, alkyl (1 to 6 carbons) or alkoxy (1 to 6 carbons) in the presence or absence of a base in an inert solvent at temperatures ranging from 0°C to 200°C to generate compounds of Formula (9). Bases may include, but are not limited to, alkali metal hydrides

- (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide, sodium ethoxide or potassium t-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine).
- 10 Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably
- 15 tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons
- 20 (preferably benzene or toluene). Preferred reaction temperatures range from ambient temperature to 100°C.
- Compounds of Formula (9) may be treated with a reducing agent in an inert solvent at -100°C to 100°C to afford products of Formula (10). Reducing agents
- 25 include, but are not limited to, (a) hydrogen gas in combination with noble metal catalysts such as Pd-on-carbon, PtO₂, Pt-on-carbon, Rh-on-alumina or Raney nickel, (b) alkali metals (preferably sodium) in combination with liquid ammonia or (c) ceric ammonium
- 30 nitrate. Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably
- 35 tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides

(preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). The preferred reaction temperatures are -50°C to 60°C. Compounds of Formula (9) are then converted to compounds of Formula (7) (where Z is N) via intermediates of Formula (11) using the reagents and reaction conditions outlined in Scheme 4 for the conversion of compounds of Formula (4) to compounds of Formula (7) (where Z is CR²).

Compounds of Formula (1) may also be prepared from compounds of Formula (7) (where Y is O, S and Z is defined above) as outlined in Scheme 6:

SCHEME 6



(7) Y = O, S; Z = N, CR²

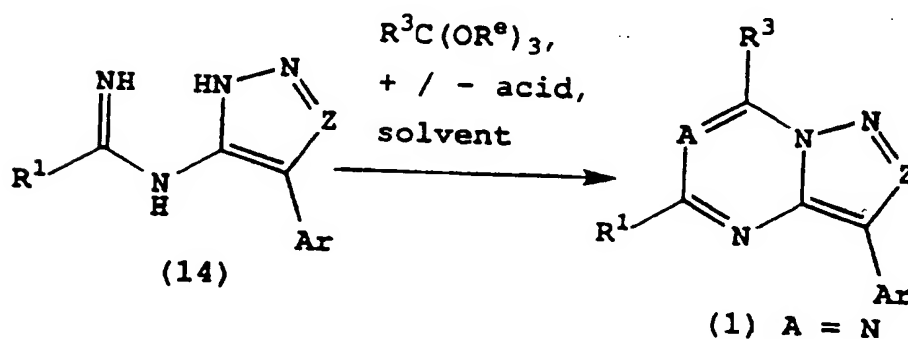
(1) A = N

Compounds of Formula (7) may be reacted with compounds of Formula R³H in the presence of a dehydrating agent in an inert solvent at reaction temperatures ranging from 0°C to 250°C. Dehydrating agents include, but are not limited to, P₂O₅, molecular sieves or inorganic or organic acids. Acids may include, but are not limited to alkanolic acids of 2 to 10 carbons (preferably acetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Inert solvents may include, but are not limited to,

alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably glyme or diglyme), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or halocarbons of 1 to 10 carbons and 1 to 10 halogens (preferably chloroform). Preferred reaction temperatures range from ambient temperature to 150°C.

Some compounds of Formula (1) (where A is N) may also be prepared by the methods shown in Scheme 7:

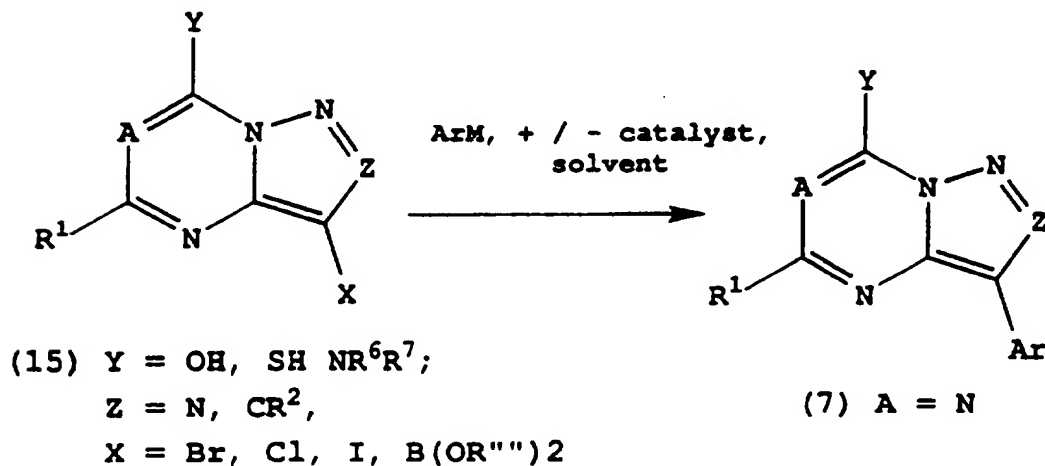
SCHEME 7



Intermediate compounds of Formula (14), where Z is defined above, may be reacted with compounds of Formula $\text{R}^3\text{C(OR}^e\text{)}_3$, where R^e may be alkyl (1 to 6 carbons) in the presence or absence of an acid in an inert solvent at temperatures ranging from 0°C to 250°C. Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or

- catalytic amounts of such acids may be used. Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 50°C to 150°C.
- Intermediate compounds of Formula (7) may also be synthesized by the reactions displayed in Scheme 8.

SCHEME 8

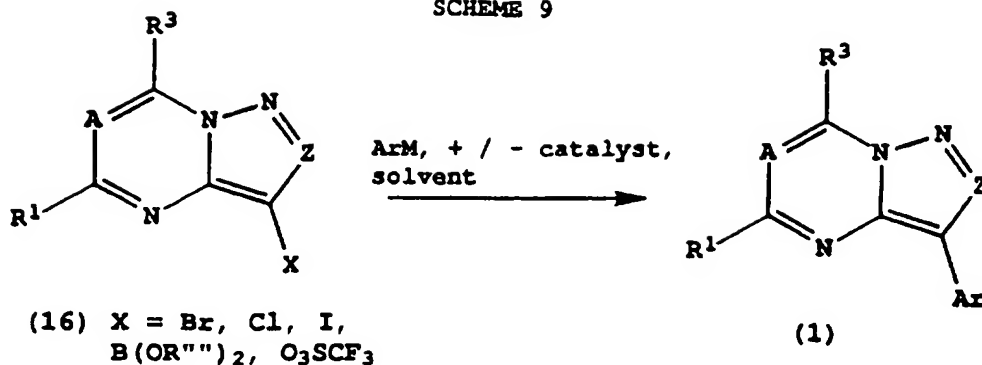


- Compounds of Formula (15), (where Y is OH, SH, NR^6R^7 ; Z is defined above, X is Br, Cl, I, O_3SCF_3 or $\text{B}(\text{OR}''')_2$ and R''' is H or alkyl (1 to 6 carbons)) may be reacted with a compound of Formula ArM (where M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, CeCl_2 , CeBr_2 or copper halides) in the presence or absence of an

- organometallic catalyst in the presence or absence of a base in an inert solvents at temperatures ranging from -100°C to 200°C. Those skilled in the art will recognize that the reagents ArM may be generated in situ. Organometallic catalysts include, but are not limited to, palladium phosphine complexes (such as $\text{Pd}(\text{PPh}_3)_4$), palladium halides or alkanoates (such as $\text{PdCl}_2(\text{PPh}_3)_2$ or $\text{Pd}(\text{OAc})_2$) or nickel complexes (such as $\text{NiCl}_2(\text{PPh}_3)_2$). Bases may include, but are not limited to, alkali metal carbonates or trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine). Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or water. Preferred reaction temperatures range from -80°C to 100°C.
- The choices of M and X are known to those skilled in the art (cf. Imamoto, T., Organocerium Reagents in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 1, 231-250; Knochel, P., Organozinc, Organocadmium and Organomercury Reagents in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 1, 211-230; Knight, D.W., Coupling Reactions between sp^2 Carbon Centers, in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 3, 481-520).

Compounds of Formula (1) may also be prepared using the methods shown in Scheme 9.

SCHEME 9

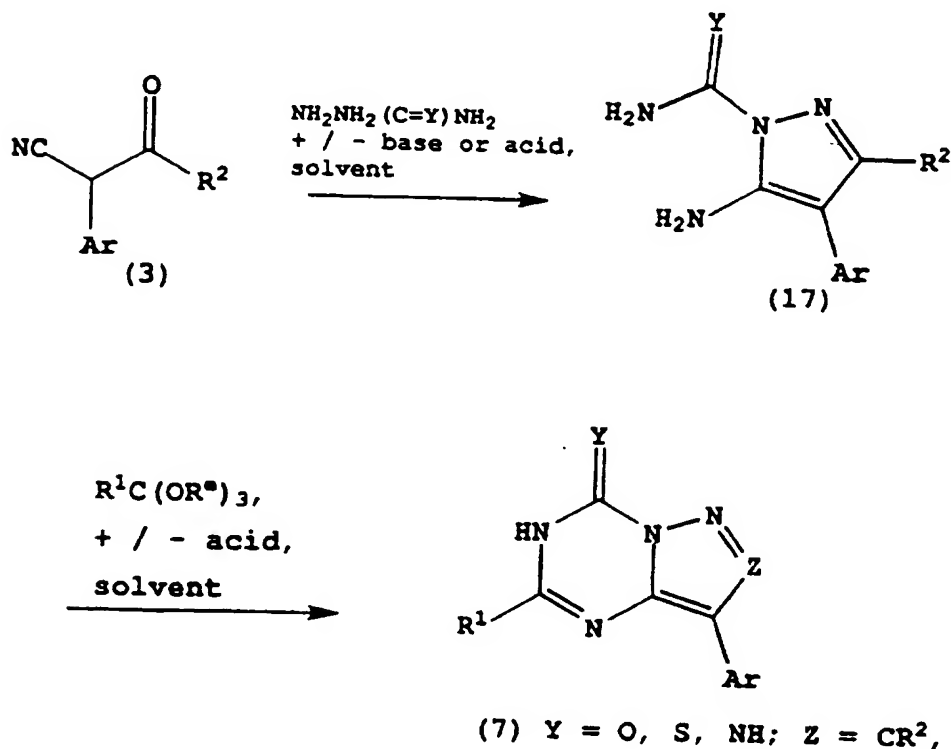


- Compounds of Formula (16), where A, Z, R¹ and R³ are defined above and X is Br, Cl, I, O₃SCF₃ or B(OR'')₂ and
- 5 R'' is H or alkyl (1 to 6 carbons)) may be reacted with a compound of Formula ArM (where M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, CeCl₂, CeBr₂ or copper halides) in the presence or absence of an organometallic catalyst in the presence or absence of a
- 10 base in an inert solvents at temperatures ranging from -100°C to 200°C. Those skilled in the art will recognize that the reagents ArM may be generated in situ (see the above references in Comprehensive Organic Synthesis). Organometallic catalysts include, but are
- 15 not limited to, palladium phosphine complexes (such as Pd(PPh₃)₄), palladium halides or alkanoates (such as PdCl₂(PPh₃)₂ or Pd(OAc)₂) or nickel complexes (such as NiCl₂(PPh₃)₂). Bases may include, but are not limited to, alkali metal carbonates or trialkyl amines
- 20 (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine). Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably
- 25 dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably

benzene or toluene) or water. Preferred reaction temperatures range from -80°C to 100°C .

Intermediate compounds of Formula (7) (where Y is O, S, NH, Z is CR^2 and R^1 , R^2 and Ar are defined as above) may be prepared as illustrated in Scheme 10.

SCHEME 10



Compounds of Formula (3) may be reacted with compounds of Formula $\text{H}_2\text{NNH}(\text{C}=\text{Y})\text{NH}_2$, where Y is O, S or NH, in the presence or absence of a base or acid in an inert solvent at temperatures from 0°C to 250°C to produce compounds of Formula (17). Acids may include, but are not limited to alkanolic acids of 2 to 10 carbons (preferably acetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts

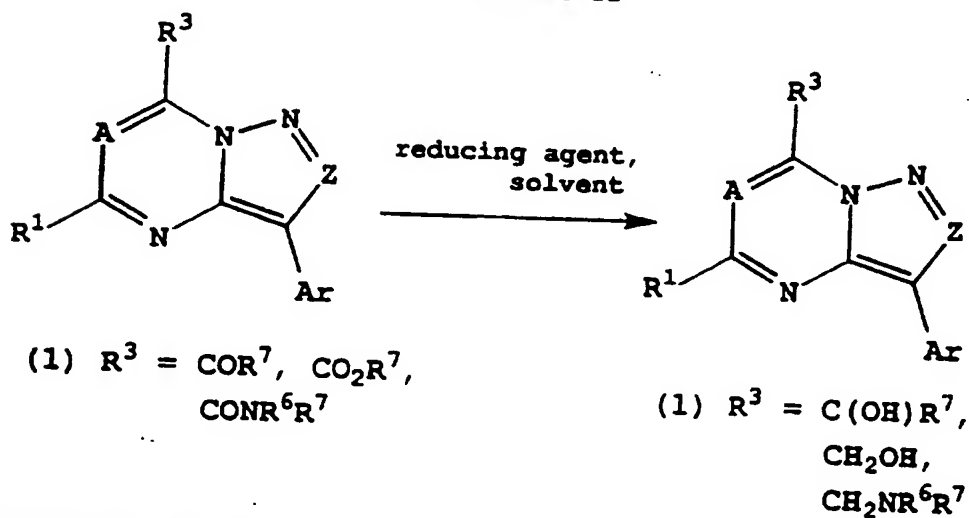
of such acids may be used. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 6 carbons), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane).

Preferred reaction temperatures range from 0°C to 150°C. Compounds of Formula (17) may then be reacted with compounds of Formula $R^3C(OR^e)_3$, where R^e may be alkyl (1 to 6 carbons) in the presence or absence of an acid in an inert solvent at temperatures ranging from 0°C to 250°C. Acids may include, but are not limited to alkanolic acids of 2 to 10 carbons (preferably acetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably

- acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane).
- 10 Preferred reaction temperatures range from 50°C to 150°C.

- In Scheme 11, the procedures which may be used to convert compounds of Formula (1), where R^3 is COR^7 , CO_2R^7 , NR^8COR^7 and $CONR^6R^7$, to other compounds of Formula (1), where R^3 is $CH(OH)R^7$, CH_2OH , $NR^8CH_2R^7$ and $CH_2NR^6R^7$ by treatment with a reducing agent in an inert solvent at temperatures ranging from -80°C to 250°C.

SCHEME 11

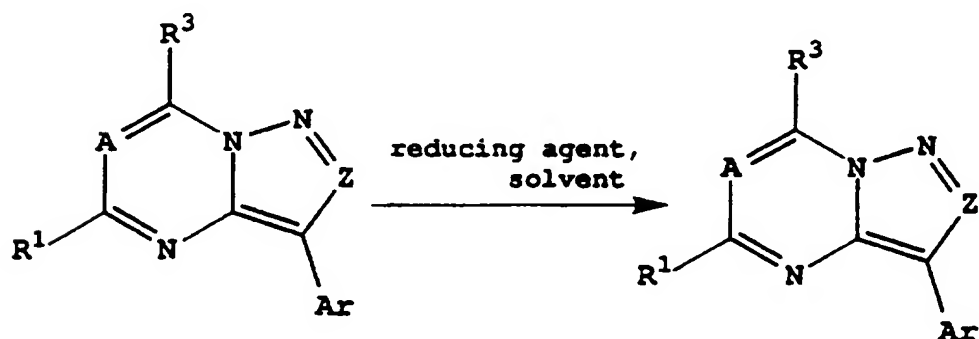


- 20 Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane, dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali
- 25 metal (trialkoxo)aluminum hydrides, or dialkyl aluminum

hydrides (such as di-isobutylaluminum hydride). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 6 carbons), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -80°C to 100°C.

In Scheme 12, the procedures are shown which may be used to convert compounds of Formula (1), where R^3 is COR^7 or CO_2R^7 , to other compounds of Formula (1), where R^3 is $C(OH)(R^7)_2$ by treatment with a reagent of Formula R^7M in an inert solvent at temperatures ranging from -80°C to 250°C.

SCHEME 12

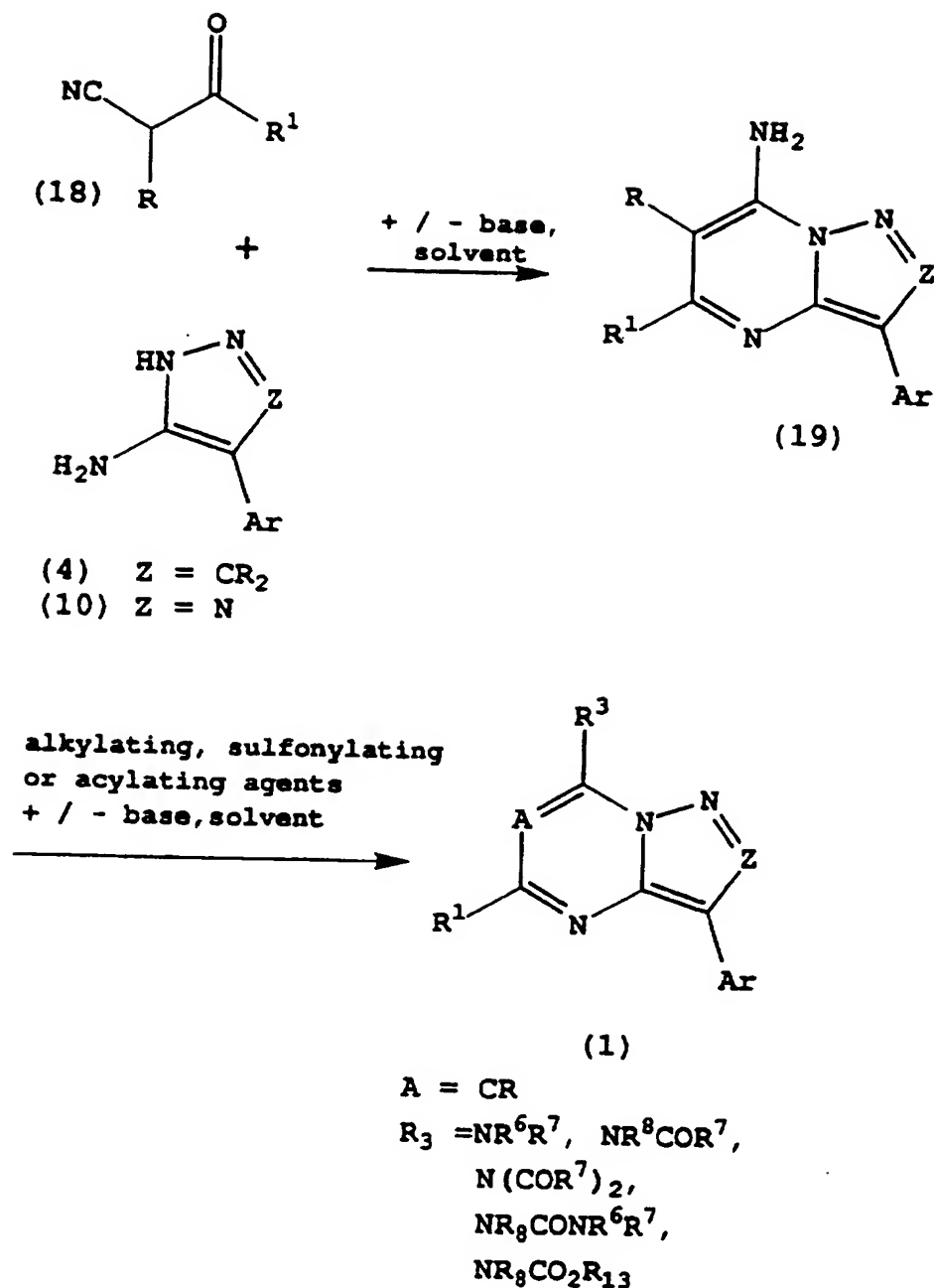


(1) $R^3 = COR^7, CO_2R^7,$ (1) $R^3 = C(OH)(R^7)_2$

M is halogen, alkali metal, $ZnCl$, $ZnBr$, ZnI , $MgBr$, $MgCl$, MgI , $CeCl_2$, $CeBr_2$ or copper halides. Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -80°C to 100°C.

Compounds of Formula (1), where R^3 may be $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-NR^8SO_2R^7$, may be synthesized as depicted in Scheme 13.

SCHEME 13



Reaction of compounds of Formula (18), where R and R¹
 5 are defined above, with compounds of Formula (4) or (10)
 in the presence or absence of base in an inert solvent
 may produce compounds of Formula (19) at temperatures

ranging from -50°C to 250°C. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

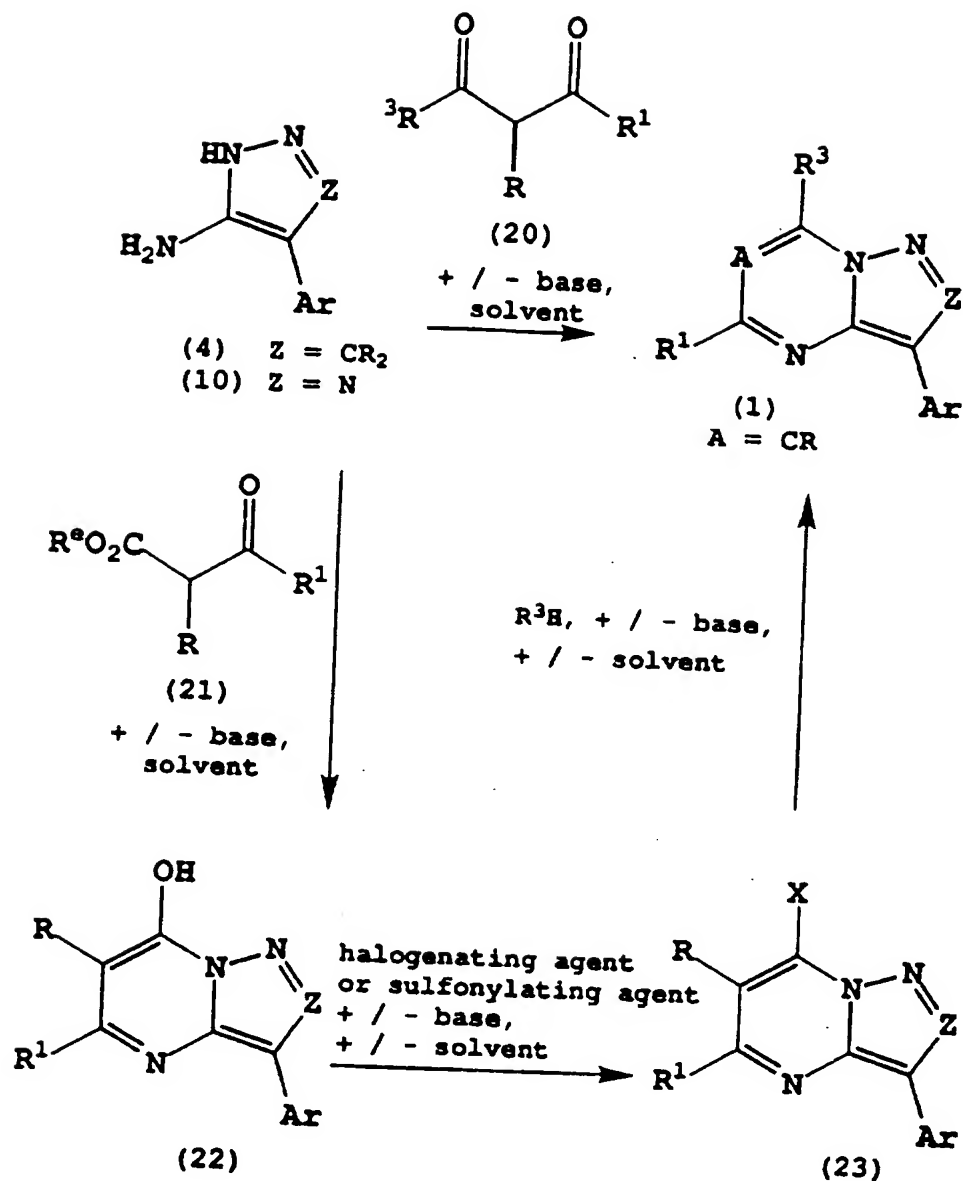
Compounds of Formula (19) may then be reacted with alkylating agents, sulfonylating agents or acylating agents or sequential reactions with combinations thereof, in the presence or absence of a base in an inert solvent at reaction temperatures ranging from -80°C to 250°C may afford compounds of Formula (1), where R^3 may be $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-NR^8SO_2R^7$. Alkylating agents may include, but are not limited to, C_1 - C_{10} alkyl -halides, -tosylates, -mesylates or -triflates; C_1 - C_{10} haloalkyl (1 - 10 halogens)-halides, -tosylates, -mesylates or -triflates; C_2 - C_8 alkoxyalkyl-halides, -tosylates, -mesylates or -triflates; C_3 - C_6 cycloalkyl-halides, -tosylates, -mesylates or -triflates; C_4 -

- C₁₂ cycloalkylalkyl-halides, -tosylates, -mesylates or -triflates; aryl(C₁-C₄ alkyl)-halides, -tosylates, -mesylates or -triflates; heteroaryl(C₁-C₄ alkyl)-halides, -tosylates, -mesylates or -triflates; or
- 5 heterocyclyl(C₁-C₄ alkyl)-halides, -tosylates, -mesylates or -triflates. Acylating agents may include, but are not limited to, C₁-C₁₀ alkanoyl halides or anhydrides, C₁-C₁₀ haloalkanoyl halides or anhydrides with 1 - 10 halogens, C₂-C₈ alkoxyalkanoyl halides or
- 10 anhydrides, C₃-C₆ cycloalkanoyl halides or anhydrides, C₄-C₁₂ cycloalkylalkanoyl halides or anhydrides, aroyl halides or anhydrides, aryl(C₁-C₄) alkanoyl halides or anhydrides, heteroaroyl halides or anhydrides, heteroaryl(C₁-C₄) alkanoyl halides or anhydrides,
- 15 heterocyclylcarboxylic acid halides or anhydrides or heterocyclyl(C₁-C₄) alkanoyl halides or anhydrides. Sulfonylating agents include, but are not limited to, C₁-C₁₀ alkylsulfonyl halides or anhydrides, C₁-C₁₀ haloalkylsulfonyl halides or anhydrides with 1 - 10
- 20 halogens, C₂-C₈ alkoxyalkylsulfonyl halides or anhydrides, C₃-C₆ cycloalkylsulfonyl halides or anhydrides, C₄-C₁₂ cycloalkylalkylsulfonyl halides or anhydrides, arylsulfonyl halides or anhydrides, aryl(C₁-C₄ alkyl)-, heteroarylsulfonyl halides or anhydrides,
- 25 heteroaryl(C₁-C₄ alkyl)sulfonyl halides or anhydrides, heterocyclylsulfonyl halides or anhydrides or heterocyclyl(C₁-C₄ alkyl)sulfonyl halides or anhydrides. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal
- 30 alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium
- 35 bis(trimethylsilyl)amide), trialkyl amines (preferably di-isopropylethyl amine) or aromatic amines (preferably

pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

Compounds of Formula (1), where A is CR and R is defined above, may be synthesized by the methods depicted in Scheme 14.

SCHEME 14



Compounds of Formula (4) or (10) may be treated with compounds of Formula (20), where R^1 and R^3 are defined above in the presence or absence of base in an inert solvent at temperatures ranging from 0°C to 250°C to give compounds of Formula (1), where A is CR and R is defined above. Bases may include, but are not limited

to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C. Alternatively, compounds of Formula (1) where A is CR and R is defined above, may be synthesized through intermediates (22) and (23).

Compounds of Formula (4) or (10) may be treated with compounds of Formula (21), where R¹ is defined above and R^e is alkyl (1 - 6 carbons), in the presence or absence of base in an inert solvent at temperatures ranging from 0°C to 250°C to give compounds of Formula (1), where A is CR and R is defined above. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium

bis(trimethylsilyl)amide), trialkyl amines (preferably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C. Compounds of Formula (22) may be treated with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to give products of Formula (23) (where X is halogen, alkanesulfonyloxy, arylsulfonyloxy or haloalkanesulfonyloxy). Halogenating agents include, but are not limited to, SOCl₂, POCl₃, PCl₃, PCl₅, POBr₃, PBr₃ or PBr₅. Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (such as methanesulfonyl chloride or methanesulfonic acid anhydride), arylsulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride) or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably

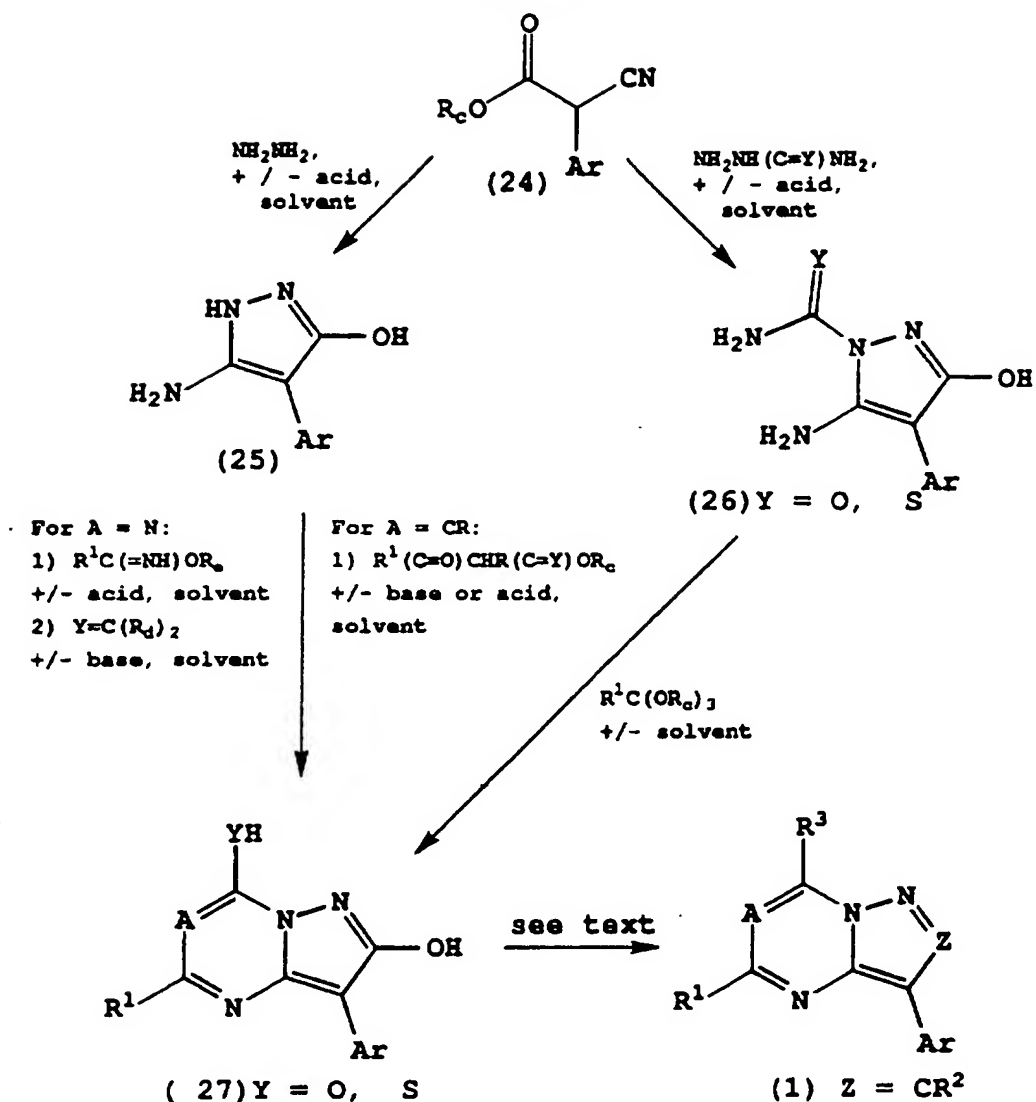
N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably
5 acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-
10 methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to
15 100°C.

Compounds of Formula (23) may be reacted with compounds of Formula R^3H (where R^3 is defined as above except R^3 is not SH, COR^7 , CO_2R^7 , aryl or heteroaryl) in the presence or absence of a base in the presence or
20 absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to generate compounds of Formula (1). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably
25 sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal
bis(trialkylsilyl)amides (preferably sodium
30 bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1
35 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably

tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 0°C to 140°C.

- 5
- 10 Some compounds of Formula (1) may also be prepared using the methods shown in Scheme 15.

SCHEME 15



- A compound of Formula (24) (R_c is a lower alkyl group and Ar is defined as above) may be reacted with
- 5 hydrazine in the presence or absence of an inert solvent to afford an intermediate of Formula (25), where Ar is defined as above. The conditions employed are similar to those used for the preparation of intermediate of Formula (4) from compound of Formula (3) in Scheme 4.
- 10 Compounds of Formula (25), where A is N, may be reacted with reagents of the formula $\text{R}^1\text{C}(=\text{NH})\text{OR}_c$, where R^1 is

defined above and R_e is a lower alkyl group) in the presence or absence of an acid in an inert solvent, followed by reaction with a compound of formula $YisC(R_d)2$ (where Y is O or S and R^d is halogen (preferably chlorine), alkoxy (1 to 4 carbons) or alkylthio (1 to 4 carbons)) in the presence or absence of a base in an inert solvent to give compounds of Formula (27) (where A is N and Y is O, S). The conditions for these transformations are the same as those employed for the conversions of compound of Formula (4) to compound of Formula (7) in Scheme 4.

Alternatively, compounds of Formula (25), where A is CR, may be reacted with compounds of the formula $R^1(C=O)CHR(C=Y)OR_c$ (where R^1 and R are defined as above and R_c is a lower alkyl group) to give a compound of Formula (27) (where A is CR) using conditions similar to those employed for the conversion of compounds of Formula (21) to compounds of Formula (22) in Scheme 14. Intermediates of Formula (27) (where Y is O) may be treated with halogenating agents or sulfonylating agents in the presence or absence of a base in an inert solvent, followed by reaction with R^3H or R^2H in the presence or absence of a base in an inert solvent to give compounds of Formula (1) (where Z is CR^2).

It will be recognized by those skilled in the art that various combinations of halogenating agents, sulfonylating agents, R^3H or R^2H may be used in different orders of reaction sequences in Scheme 15 to afford compounds of Formula (1). For example, in some cases, it may be desirable to react compounds with stoichiometric amounts of halogenating agents or sulfonylating agents, react with R^2H (or R^3H), then repeat the reaction with halogenating agents or sulfonylating agents and react with R^3H (or R^2H) to give compounds of Formula (1). The reaction conditions and reagents used for these conversions are similar to the

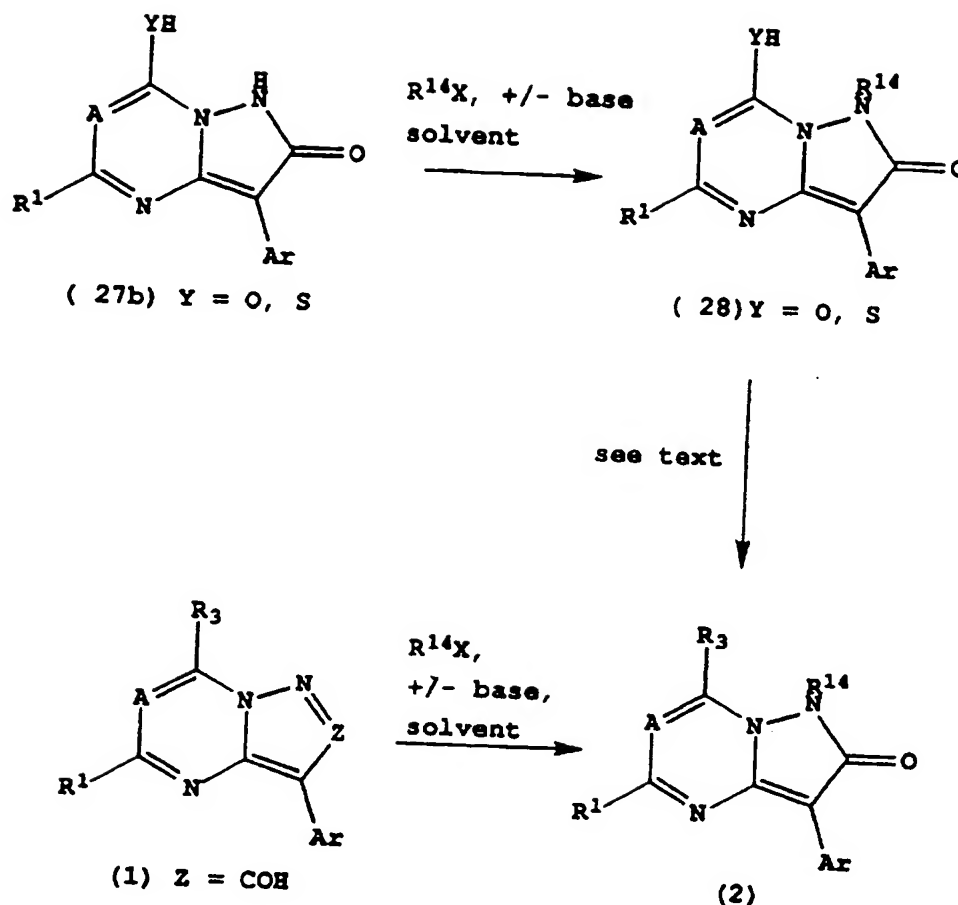
ones employed for the conversion of intermediate compounds of Formulae (22) to (23) to (1) in Scheme 14 (for A is CR) or the conversion of intermediate compounds of Formulae (7) to (8) to (1) in Scheme 1
5 (where A is N).

Alternatively, compounds of Formula (27) (where Y is S) may be converted to compounds of Formula (1) in Scheme 15. Intermediate compounds of Formula (27) may be alkylated with a compound R^fX (where R^f is lower
10 alkyl and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in an inert solvent, (then optionally oxidized with an oxidizing agent in an inert solvent) and then reacted with R^3H in the presence or absence of a base in an inert solvent to give a compound
15 of Formula (1). The conditions and reagents employed are similar to those used in the conversion of intermediate compounds of Formulae (7) to (12) (or to (13)) to compounds of Formula (1) in Scheme 2.

Compounds of Formula (1) may be prepared from
20 compounds of Formula (24), using an alternate route as depicted in Scheme 15. Compounds of Formula (24) may be converted to compounds of Formula (27) via reaction with compounds of formula $NH_2NH(C=NH)NH_2$ in the presence or absence of an acid in an inert solvent, followed by
25 reaction with compounds $R^1C(OR_C)_3$ (where R_C is lower alkyl and R^1 is defined as above), using the conditions employed for the conversion of compounds of Formulae (3) to (17) to (7) in Scheme 10.

Some compounds of Formula (2) may be prepared by
30 the methods illustrated in Scheme 16.

SCHEME 16



Compounds of Formula (27b) may be treated with various alkylating agents $R^{14}X$ (where R^{14} is defined above and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in the presence or absence of a base in an inert solvent to afford structures of Formula (28). Compounds of Formula (28) (Y is O) may then be converted to compounds of Formula (2) by treatment with halogenating agents or sulfonylating agents in the presence or absence of a base in an inert solvent, followed by reaction with R^3H in the presence or absence of a base in an inert solvent to give compounds of Formula (2). The reaction conditions used for these conversions are similar to the

ones employed for the conversion of intermediate compounds (22) to (23) to (1) in Scheme 14 (for A is CR) or the conversion of intermediate compounds of Formulae (7) to (8) to (1) in Scheme 1 (where A is N).

- 5 Alternatively, compounds of Formula (28) (Y is S) may be alkylated with a compound R^fX (where R^f is lower alkyl and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in an inert solvent, (then optionally oxidized with an oxidizing agent in an inert solvent) and then reacted with R^3H in the presence or
10 absence of a base in an inert solvent to give a compound of Formula (1). The conditions and reagents employed are similar to those used in the conversion of intermediate compounds of Formulae (7) to (12) (or to
15 (13)) to compounds of Formula (1) in Scheme 2.

Compounds of Formula (1), where Z is COH, may be converted to compounds of Formula (2) as illustrated in Scheme 16. Treatment with various alkylating agents $R^{14}X$ (where R^{14} is defined above and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in the
20 presence or absence of a base in an inert solvent to afford structures (2). It will be recognized by one skilled in the art that the methods used in Scheme 16 may also be used to prepare compounds of Formula (1)
25 where Z is COR^7 .

For Scheme 16, the terms "base" and "inert solvent" may have the meanings given below. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1
30 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably
35 N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents

may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to 100°C.

15

EXAMPLES

Analytical data were recorded for the compounds described below using the following general procedures.

20 Proton NMR spectra were recorded on an IBM-Bruker FT-NMR (300 MHz); chemical shifts were recorded in ppm (δ) from an internal tetramethylsilane standard in deuteriochloroform or deuterodimethylsulfoxide as specified below. Mass spectra (MS) or high resolution

25 mass spectra (HRMS) were recorded on a Finnegan MAT 8230 spectrometer (using chemi-ionization (CI) with NH_3 as the carrier gas or gas chromatography (GC) as specified below) or a Hewlett Packard 5988A model spectrometer. Melting points were recorded on a Buchi Model 510

30 melting point apparatus and are uncorrected. Boiling points are uncorrected. All pH determinations during workup were made with indicator paper.

Reagents were purchased from commercial sources and, where necessary, purified prior to use according to

35 the general procedures outlined by D. Perrin and W.L.F. Armarego, *Purification of Laboratory Chemicals*, 3rd ed., (New York: Pergamon Press, 1988). Chromatography was

performed on silica gel using the solvent systems indicated below. For mixed solvent systems, the volume ratios are given. Otherwise, parts and percentages are by weight.

5

The following examples are provided to describe the invention in further detail. These examples, which set forth the best mode presently contemplated for carrying out the invention, are intended to illustrate and not to limit the invention.

EXAMPLE 1

Preparation of

2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]
-pyrazolo-[1,3,5]-triazin-4(3H)-one
(Formula 7, where Y is O, R₁ is CH₃, Z is C-CH₃,
Ar is 2,4-dimethylphenyl)

A. 1-Cyano-1-(2,4-dimethylphenyl)propan-2-one

Sodium pellets (9.8g, 0.43 mol) were added portionwise to a solution of 2,4-dimethylphenylacetonitrile (48 g, 0.33 mol) in ethyl acetate (150 mL) at ambient temperature. The reaction mixture was heated to reflux temperature and stirred for 16 hours. The resulting suspension was cooled to room temperature and filtered. The collected precipitate was washed with copious amounts of ether and then air-dried. The solid was dissolved in water and a 1N HCl solution was added until the pH = 5-6. The mixture was extracted with ethyl acetate (3 X 200 mL); the combined organic layers were dried over MgSO₄ and filtered. Solvent was removed *in vacuo* to afford a white solid (45.7g, 74% yield): NMR (CDCl₃, 300 MHz): δ 1.8 (s, 6H), 2.1 (s, 3H), 2.4 (s, 3H), 2.6 (s, 3H), 2.8 (s, 3H), 3.1 (s, 3H), 3.2 (s, 3H), 3.3 (s, 3H), 3.4 (s, 3H), 3.5 (s, 3H), 3.6 (s, 3H), 3.7 (s, 3H), 3.8 (s, 3H), 3.9 (s, 3H), 4.0 (s, 3H), 4.1 (s, 3H), 4.2 (s, 3H), 4.3 (s, 3H), 4.4 (s, 3H), 4.5 (s, 3H), 4.6 (s, 3H), 4.7 (s, 3H), 4.8 (s, 3H), 4.9 (s, 3H), 5.0 (s, 3H), 5.1 (s, 3H), 5.2 (s, 3H), 5.3 (s, 3H), 5.4 (s, 3H), 5.5 (s, 3H), 5.6 (s, 3H), 5.7 (s, 3H), 5.8 (s, 3H), 5.9 (s, 3H), 6.0 (s, 3H), 6.1 (s, 3H), 6.2 (s, 3H), 6.3 (s, 3H), 6.4 (s, 3H), 6.5 (s, 3H), 6.6 (s, 3H), 6.7 (s, 3H), 6.8 (s, 3H), 6.9 (s, 3H), 7.0 (s, 3H), 7.1 (s, 3H), 7.2 (s, 3H), 7.3 (s, 3H), 7.4 (s, 3H), 7.5 (s, 3H), 7.6 (s, 3H), 7.7 (s, 3H), 7.8 (s, 3H), 7.9 (s, 3H), 8.0 (s, 3H), 8.1 (s, 3H), 8.2 (s, 3H), 8.3 (s, 3H), 8.4 (s, 3H), 8.5 (s, 3H), 8.6 (s, 3H), 8.7 (s, 3H), 8.8 (s, 3H), 8.9 (s, 3H), 9.0 (s, 3H), 9.1 (s, 3H), 9.2 (s, 3H), 9.3 (s, 3H), 9.4 (s, 3H), 9.5 (s, 3H), 9.6 (s, 3H), 9.7 (s, 3H), 9.8 (s, 3H), 9.9 (s, 3H). CI-MS: 188 (M + H).

35

B. 5-Amino-4-(2,4-dimethylphenyl)-3-methylpyrazole

A mixture of 1-cyano-1-(2,4-dimethylphenyl)propan-2-one (43.8g, 0.23 mol), hydrazine-hydrate (22 mL, 0.46 mol), glacial acetic acid (45 mL, 0.78 mol) and toluene (500 mL) were stirred at reflux temperature for 18 hours in an apparatus fitted with a Dean-Stark trap. The reaction mixture was cooled to ambient temperature and solvent was removed in vacuo. The residue was dissolved in 6N HCl and the resulting solution was extracted with ether three times. A concentrated ammonium hydroxide solution was added to the aqueous layer until pH = 11. The resulting semi-solution was extracted three times with ethyl acetate. The combined organic layers were dried over MgSO₄ and filtered. Solvent was removed in vacuo to give a pale brown viscous oil (34.6g, 75% yield): NMR (CDCl₃, 300 MHz): 7.10 (s, 1H), 7.05 (d, 2H, J=1), 2.37 (s, 3H), 2.10 (s, 3H); CI-MS: 202 (M + H).

C. 5-Acetamidino-4-(2,4-dimethylphenyl)-3-methylpyrazole, acetic acid salt

Ethyl acetamidate hydrochloride (60g, 0.48 mol) was added quickly to a rapidly stirred mixture of potassium carbonate (69.5g, 0.50 mol), dichloromethane (120 mL) and water (350 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 X 120 mL). The combined organic layers were dried over MgSO₄ and filtered. Solvent was removed by simple distillation and the pot residue, a clear pale yellow liquid, (35.0 g) was used without further purification.

Glacial acetic acid (9.7 mL, 0.17 mol) was added to a stirred mixture of 5-amino-4-(2,4-dimethylphenyl)-3-methylpyrazole (34g, 0.17 mol), ethyl acetamidate (22g, 0.25 mol) and acetonitrile (500 mL). The resulting reaction mixture was stirred at room temperature for 3 days; at the end of which time, it was concentrated in vacuo to about one-third of its original volume. The resulting suspension was filtered and the collected

solid was washed with copious amounts of ether. The white solid was dried *in vacuo* (31.4g, 61% yield): NMR (DMSO- d_6 , 300 MHz): 7.00 (s, 1H), 6.90 (dd, 2H, $J=7, 1$), 2.28 (s, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 1.90 (s, 3H), 1.81 (s, 3H); CI-MS: 243 (M + H).

D. 2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-[1,3,5]-triazin-4(3H)-one

Sodium pellets (23g, 1 mol) were added portionwise to ethanol (500 mL) with vigorous stirring. After all the sodium reacted, 5-acetamidino-4-(2,4-dimethylphenyl)-3-methylpyrazole, acetic acid salt (31.2g, 0.1 mol) and diethyl carbonate (97 mL, 0.8 mol) were added. The resulting reaction mixture was heated to reflux temperature and stirred for 18 hours. The mixture was cooled to room temperature and solvent was removed *in vacuo*. The residue was dissolved in water and a 1N HCl solution was added slowly until pH = 5-6. The aqueous layer was extracted with ethyl acetate three times; the combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a pale tan solid (26g, 98% yield): NMR ($CDCl_3$, 300 MHz): 7.15 (s, 1H), 7.09 (s, 2H), 2.45 (s, 3H), 2.39 (s, 3H), 2.30 (s, 3H); CI-MS: 269 (M + H).

EXAMPLE 2

Preparation of

5-methyl-3-(2,4,6-trimethylphenyl)[1,5-a]-[1,2,3]-triazolo-[1,3,5]-triazin-7(6H)-one
(Formula 7, where Y is O, R_1 is CH_3 , Z is N, Ar is 2,4,6-trimethylphenyl)

A. 1-Phenylmethyl-4-(2,4,6-trimethylphenyl)-5-aminotriazole

A mixture of 2,4,6-trimethylbenzyl cyanide (1.0g, 6.3 mmol), benzyl azide (0.92g, 6.9 mmol) and potassium

t-butoxide (0.78g, 6.9 mmol) in tetrahydrofuran (10mL) was stirred at ambient temperature for 2.5 days. The resulting suspension was diluted with water and extracted three times with ethyl acetate. The combined organic layers were dried over MgSO₄ and filtered. Solvent was removed in vacuo to give a brown oil. Trituration with ether and filtration afforded a yellow solid (1.12g, 61% yield): NMR (CDCl₃, 300 MHz): 7.60-7.30 (m, 5H), 7.30-7.20 (m, 2H), 5.50 (s, 2H), 3.18 (br s, 2H), 2.30 (s, 3H), 2.10 (s, 6H); CI-MS: 293 (M + H).

B. 4-(2,4,6-Trimethylphenyl)-5-aminotriazole

Sodium (500 mg, 22 mmol) was added with stirring to a mixture of liquid ammonia (30 mL) and 1-phenylmethyl-4-(2,4,6-trimethylphenyl)-5-aminotriazole (1.1g, 3.8 mmol). The reaction mixture was stirred until a dark green color persisted. An ammonium chloride solution (mL) was added and the mixture was stirred while warming to ambient temperature over 16 hours. The residue was treated with a 1M HCl solution and filtered. The aqueous layer was basified with a concentrated ammonium hydroxide solution (pH = 9) and then extracted with ethyl acetate three times. The combined organic layers were dried over MgSO₄ and filtered. Solvent was removed in vacuo to give a yellow solid (520 mg), which was homogeneous by thin layer chromatography (ethyl acetate): NMR (CDCl₃, 300 MHz): 6.97 (s, 2H), 3.68-3.50 (br.s, 2H), 2.32 (s, 3H), 2.10 (s, 6H); CI-MS: 203 (M + H).

C. 4-(2,4,6-Trimethylphenyl)-5-acetamidinotriazole, acetic acid salt

A mixture of 4-(2,4,6-trimethylphenyl)-5-aminotriazole (400 mg, 1.98 mmol), ethyl acetamidate (261 mg, 3 mmol) and glacial acetic acid (0.1 mL, 1.98 mmol) in acetonitrile (6 mL) was stirred at ambient

temperature for 4 hours. The resulting suspension was filtered and the collected solid was washed with copious amounts of ether. Drying *in vacuo* afforded a white solid (490 mg, 82% yield): NMR (DMSO- d_6 , 300 MHz): 7.90-7.70 (br s, 0.5H), 7.50-7.20 (br. s, 0.5H), 6.90 (s, 2H), 6.90 (s, 2H), 3.50-3.10 (br s, 3H), 2.30-2.20 (br s, 3H), 2.05 (d, 1H, $J = 7$), 1.96 (s, 6H), 1.87 (s, 6H); CI-MS: 244 (M + H).

- 10 D. 5-methyl-3-(2,4,6-trimethylphenyl)[1,5-a]-[1,2,3]-triazolo-[1,3,5]-triazin-7(4H)-one
Sodium (368 mg, 16.2 mmol) was added with stirring to ethanol (10 mL) at room temperature. After the sodium had reacted, 4-(2,4,6-trimethylphenyl)-5-
15 acetamidino-triazole, acetic acid salt (490 mg, 1.6 mmol) and diethyl carbonate (1.6 mL, 13 mmol) were added. The reaction mixture was stirred at reflux temperature for 5 hours, then cooled to room temperature. The reaction mixture was diluted with
20 water; a 1N HCl solution was added until pH = 5-6 and three extractions with ethyl acetate were performed. The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a yellow residue. Trituration with ether and filtration afforded
25 a yellow solid (300 mg, 69% yield): NMR ($CDCl_3$, 300 MHz): 6.98 (s, 2H), 2.55 (s, 3H), 2.35 (s, 3H), 2.10 (s, 6H); CI-MS: 270 (M + H).

EXAMPLE 3

- 30 Preparation of 4-(di(carbomethoxy)methyl)-2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazine
(Formula 1, where R^3 is $CH(CHCO_2CH_3)_2$, R_1 is CH_3 , Z is C- CH_3 , Ar is 2,4-dimethylphenyl)

35

A. 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolotriazine

A mixture of 2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]

5 -pyrazolo-1,3,5-triazin-4-one (Example 1, 1.38g, 4.5 mmol), N,N-dimethylaniline (1 mL, 8 mmol) and phosphorus oxychloride (10 mL) was stirred at reflux temperature for 48 hours. The excess phosphorus oxychloride was removed *in vacuo*. The residue was poured onto ice-
10 water, stirred briefly and extracted quickly with ethyl acetate three times. The combined organic layers were washed with ice water, then dried over MgSO₄ and filtered. Solvent was removed *in vacuo* to give a brown oil. Flash column chromatography (ethyl
15 acetate:hexanes::1:4) gave one fraction (R_f = 0.5). Solvent was removed *in vacuo* to afford a yellow oil (1.0g, 68% yield): NMR (CDCl₃, 300 MHz): 7.55 (d, 1H, J = 1), 7.38 (dd, 1H, J = 7, 1), 7.30 (d, 1H, J = 7), 2.68 (s, 3H), 2.45 (s, 3H); CI-MS: 327 (M + H).

20

B. 4-(di(carbomethoxy)methyl)-2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazine

Sodium hydride (60% in oil, 80 mg, 2 mmol) was washed with hexanes twice, decanted after each washing
25 and taken up in anhydrous tetrahydrofuran (THF, 1 mL). A solution of diethyl malonate (0.32g, 2 mmol) in THF (2 mL) was added dropwise over 5 min, during which time vigorous gas evolution ensued. A solution of 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-
30 pyrazolotriazine (0.5g, 1.75 mmol) in THF (2 mL) was added and the reaction mixture was then stirred under a nitrogen atmosphere for 48 hours. The resulting suspension was poured onto water and extracted three
35 times with ethyl acetate. The combined organic layers were washed once with brine, dried over MgSO₄ and filtered. Solvent was removed *in vacuo* to give a brown

oil. Column chromatography (ethyl acetate:hexanes::1:9) afforded, after removal of solvent *in vacuo*, a pale yellow solid ($R_f = 0.2$, 250 mg, 35% yield): mp 50-52°C; NMR ($CDCl_3$, 300 MHz): 12.35 (br.s, 1H, 7.15-7.00 (m, 3H), 4.40 (q, 2H, $J = 7$), 4.30 (q, 2H, $J = 7$), 2.4, 2.35, 2.3, 2.2, 2.1 (5 s, 12H), 1.4 (t, 3H, $J = 7$), 1.35-1.25 (m, 3H); CI-HRMS: Calcd: 411.2032, Found: 411.2023.

10

EXAMPLE 6

Preparation of 4-(1,3-dimethoxy-2-propylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolo-1,3,5-triazine

15 (Formula 1, where R^3 is $NHCH(CH_2OCH_3)_2$, R_1 is CH_3 , Z is $C-CH_3$, Ar is 2,4-dichlorophenyl)

A. 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolotriazine

20 A mixture of 2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazin-4-one (Example 1, 1.38g, 4.5 mmol), *N,N*-dimethylaniline (1 mL, 8 mmol) and phosphorus oxychloride (10 mL) was stirred at reflux temperature for 48 hours. The excess
25 phosphorus oxychloride was removed *in vacuo*. The residue was poured onto ice-water, stirred briefly and extracted quickly with ethyl acetate three times. The combined organic layers were washed with ice water, then dried over $MgSO_4$ and filtered. Solvent was removed *in*
30 *vacuo* to give a brown oil. Flash column chromatography (ethyl acetate:hexanes::1:4) gave one fraction ($R_f = 0.5$). Solvent was removed *in vacuo* to afford a yellow oil (1.0g, 68% yield): NMR ($CDCl_3$, 300 MHz): 7.55 (d, 1H, $J = 1$), 7.38 (dd, 1H, $J = 7, 1$), 7.30 (d, 1H, $J = 7$),
35 2.68 (s, 3H), 2.45 (s, 3H); CI-MS: 327 ($M + H$).

B. 4-(1,3-dimethoxy-2-propylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolo-1,3,5-triazine

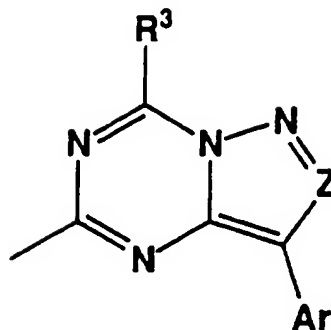
A mixture of 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolo-1,3,5-triazine (Part A, 570 mg, 1.74 mmol), 1,3-dimethoxypropyl-2-aminopropane (25mg, 2.08 mmol) and ethanol (10 mL) was stirred at ambient temperature for 18 hours. The reaction mixture was poured onto water (25 mL) and extracted three times with ethyl acetate. The combined organic layers were dried over MgSO_4 and filtered. Solvent was removed *in vacuo*. Column chromatography ($\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}::50:1$) afforded one fraction. Removal of solvent *in vacuo* gave a solid (250 mg, 35% yield): mp 118-120°C; NMR (CDCl_3 , 300 MHz): 7.50 (s, 1H), 7.28 (dd, 2H, $J = 8, 1$), 6.75 (d, 1H, $J = 8$), 4.70-4.58 (m, 1H), 3.70-3.55 (m, 4H), 3.43 (s, 6H), 2.50 (s, 3H), 2.35 (s, 3H); CI-HRMS: Calcd: 409.1072, Found: 409.1085; Analysis Calcd. for $\text{C}_{18}\text{H}_{21}\text{Cl}_2\text{N}_5\text{O}_2$: C, 52.69, H, 5.17, N, 17.07, Cl, 17.28; Found: C, 52.82, H, 5.06, N, 16.77, Cl, 17.50.

Using the above procedures and modifications known to one skilled in the art of organic synthesis, the following additional examples of Tables 1-4 may be prepared.

The examples delineated in TABLE 1 may be prepared by the methods outlined in Examples 1, 2, 3 or 6.

Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example.

TABLE 1



| 5 | Ex. | Z | R ₃ | Ar | mp (°C) |
|----|-----------------|------|--|-------------------------|---------|
| | 6 ^a | C-Me | NHCH(CH ₂ OMe) ₂ | 2,4-Cl ₂ -Ph | 118-120 |
| | 7 ^b | C-Me | NHCHPr ₂ | 2,4-Cl ₂ -Ph | 114-116 |
| | 8 ^c | C-Me | NEtBu | 2,4-Cl ₂ -Ph | oil |
| | 9 ^d | C-Me | NPr(CH ₂ -c-C ₃ H ₅) | 2,4-Cl ₂ -Ph | oil |
| 10 | 10 ^e | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2,4-Cl ₂ -Ph | oil |
| | 11 ^f | C-Me | NH-3-heptyl | 2,4-Cl ₂ -Ph | 90-92 |
| | 12 ^g | C-Me | NHCH(Et)CH ₂ OMe | 2,4-Cl ₂ -Ph | 179-181 |
| | 13 ^h | C-Me | NEt ₂ | 2,4-Cl ₂ -Ph | 133-134 |
| | 14 ⁱ | C-Me | NHCH(CH ₂ OEt) ₂ | 2,4-Cl ₂ -Ph | oil |
| 15 | 15 ^j | C-Me | NH-3-pentyl | 2,4-Cl ₂ -Ph | 139-140 |
| | 16 ^k | C-Me | NMePh | 2,4-Cl ₂ -Ph | 60-62 |
| | 17 ^l | C-Me | NPr ₂ | 2,4-Cl ₂ -Ph | oil |
| | 18 ^m | C-Me | NH-3-hexyl | 2,4-Cl ₂ -Ph | 130-132 |
| | 19 | C-Me | morpholino | 2,4-Cl ₂ -Ph | |
| 20 | 20 | C-Me | N(CH ₂ Ph)CH ₂ CH ₂ OMe | 2,4-Cl ₂ -Ph | |
| | 21 | C-Me | NHCH(CH ₂ Ph)CH ₂ OMe | 2,4-Cl ₂ -Ph | |
| | 22 | C-Me | NH-4-tetrahydropyranyl | 2,4-Cl ₂ -Ph | |
| | 23 | C-Me | NH-cyclopentyl | 2,4-Cl ₂ -Ph | |
| | 24 | C-Me | 1,2,3,4-tetrahydro- | 2,4-Cl ₂ -Ph | |
| 25 | | | isoquinolinyl | | |
| | 25 | C-Me | CH ₂ -(1,2,3,4-tetrahydro- | 2,4-Cl ₂ -Ph | |
| | | | isoquinolinyl) | | |
| | 26 ⁿ | C-Me | OEt | 2,4-Cl ₂ -Ph | 141-143 |
| | 27 | C-Me | OCH(Et)CH ₂ OMe | 2,4-Cl ₂ -Ph | |

| | | | | | |
|----|------------------|------|--|---------------------------|---------|
| | 28 | C-Me | OCH ₂ Ph | 2,4-Cl ₂ -Ph | |
| | 29 | C-Me | O-3-pentyl | 2,4-Cl ₂ -Ph | |
| | 30 | C-Me | SEt | 2,4-Cl ₂ -Ph | |
| | 31 | C-Me | S(O)Et | 2,4-Cl ₂ -Ph | |
| 5 | 32 | C-Me | SO ₂ Et | 2,4-Cl ₂ -Ph | |
| | 33 | C-Me | CH(CO ₂ Et) ₂ | 2,4-Cl ₂ -Ph | |
| | 34 | C-Me | C(Et)(CO ₂ Et) ₂ | 2,4-Cl ₂ -Ph | |
| | 35 | C-Me | CH(Et)CH ₂ OH | 2,4-Cl ₂ -Ph | |
| | 36 | C-Me | CH(Et)CH ₂ OMe | 2,4-Cl ₂ -Ph | |
| 10 | 37 | C-Me | CONMe ₂ | 2,4-Cl ₂ -Ph | |
| | 38 | C-Me | COCH ₃ | 2,4-Cl ₂ -Ph | |
| | 39 | C-Me | CH(OH)CH ₃ | 2,4-Cl ₂ -Ph | |
| | 40 | C-Me | C(OH)Ph-3-pyridyl | 2,4-Cl ₂ -Ph | |
| | 41 | C-Me | Ph | 2,4-Cl ₂ -Ph | |
| 15 | 42 | C-Me | 2-CF ₃ -Ph | 2,4-Cl ₂ -Ph | |
| | 43 | C-Me | 2-Ph-Ph | 2,4-Cl ₂ -Ph | |
| | 44 | C-Me | 3-pentyl | 2,4-Cl ₂ -Ph | |
| | 45 | C-Me | cyclobutyl | 2,4-Cl ₂ -Ph | |
| | 46 | C-Me | 3-pyridyl | 2,4-Cl ₂ -Ph | |
| 20 | 47 | C-Me | CH(Et)CH ₂ CONMe ₂ | 2,4-Cl ₂ -Ph | |
| | 48 | C-Me | CH(Et)CH ₂ CH ₂ NMe ₂ | 2,4-Cl ₂ -Ph | |
| | 49 ^o | C-Me | NHCH(CH ₂ OMe) ₂ | 2,4,6-Me ₃ -Ph | 125-127 |
| | 50 | C-Me | NHCHPr ₂ | 2,4,6-Me ₃ -Ph | |
| | 51 | C-Me | NEtBu | 2,4,6-Me ₃ -Ph | |
| 25 | 52 | C-Me | NPr(CH ₂ -c-C ₃ H ₅) | 2,4,6-Me ₃ -Ph | |
| | 53 ^{ae} | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2,4,6-Me ₃ -Ph | 123-124 |
| | 54 | C-Me | NH-3-heptyl | 2,4,6-Me ₃ -Ph | |
| | 55 ^{ac} | C-Me | NHCH(Et)CH ₂ OMe | 2,4,6-Me ₃ -Ph | 145-146 |
| | 56 ^{ah} | C-Me | NEt ₂ | 2,4,6-Me ₃ -Ph | 88-90 |
| 30 | 57 ^{ai} | C-Me | NHCH(CH ₂ OEt) ₂ | 2,4,6-Me ₃ -Ph | 132-134 |
| | 58 ^{ad} | C-Me | NH-3-pentyl | 2,4,6-Me ₃ -Ph | 134-135 |
| | 59 | C-Me | NMePh | 2,4,6-Me ₃ -Ph | |
| | 60 | C-Me | NPr ₂ | 2,4,6-Me ₃ -Ph | |
| | 61 | C-Me | NH-3-hexyl | 2,4,6-Me ₃ -Ph | |
| 35 | 62 | C-Me | morpholino | 2,4,6-Me ₃ -Ph | |
| | 63 | C-Me | N(CH ₂ Ph)CH ₂ CH ₂ OMe | 2,4,6-Me ₃ -Ph | |

| | | | | | |
|----|-----------------|------|--|---------------------------|---------|
| | 64 | C-Me | NHCH(CH ₂ Ph)CH ₂ OMe | 2,4,6-Me ₃ -Ph | |
| | 65 | C-Me | NH-4-tetrahydropyranyl | 2,4,6-Me ₃ -Ph | |
| | 66 | C-Me | NH-cyclopentyl | 2,4,6-Me ₃ -Ph | |
| | 67 | C-Me | 1,2,3,4-tetrahydro- | 2,4,6-Me ₃ -Ph | |
| 5 | | | isoquinolinyl | | |
| | 68 | C-Me | CH ₂ -(1,2,3,4-tetrahydro- | 2,4,6-Me ₃ -Ph | |
| | | | isoquinolinyl) | | |
| | 69 | C-Me | OEt | 2,4,6-Me ₃ -Ph | |
| | 70 | C-Me | OCH(Et)CH ₂ OMe | 2,4,6-Me ₃ -Ph | |
| 10 | 71 | C-Me | OCH ₂ Ph | 2,4,6-Me ₃ -Ph | |
| | 72 | C-Me | O-3-pentyl | 2,4,6-Me ₃ -Ph | |
| | 73 | C-Me | SEt | 2,4,6-Me ₃ -Ph | |
| | 74 | C-Me | S(O)Et | 2,4,6-Me ₃ -Ph | |
| | 75 | C-Me | SO ₂ Et | 2,4,6-Me ₃ -Ph | |
| 15 | 76 | C-Me | CH(CO ₂ Et) ₂ | 2,4,6-Me ₃ -Ph | |
| | 77 | C-Me | C(Et)(CO ₂ Et) ₂ | 2,4,6-Me ₃ -Ph | |
| | 78 | C-Me | CH(Et)CH ₂ OH | 2,4,6-Me ₃ -Ph | |
| | 79 | C-Me | CH(Et)CH ₂ OMe | 2,4,6-Me ₃ -Ph | |
| | 80 | C-Me | CONMe ₂ | 2,4,6-Me ₃ -Ph | |
| 20 | 81 | C-Me | COCH ₃ | 2,4,6-Me ₃ -Ph | |
| | 82 | C-Me | CH(OH)CH ₃ | 2,4,6-Me ₃ -Ph | |
| | 83 | C-Me | C(OH)Ph-3-pyridyl | 2,4,6-Me ₃ -Ph | |
| | 84 | C-Me | Ph | 2,4,6-Me ₃ -Ph | |
| | 85 | C-Me | 2-CF ₃ -Ph | 2,4,6-Me ₃ -Ph | |
| 25 | 86 | C-Me | 2-Ph-Ph | 2,4,6-Me ₃ -Ph | |
| | 87 | C-Me | 3-pentyl | 2,4,6-Me ₃ -Ph | |
| | 88 | C-Me | cyclobutyl | 2,4,6-Me ₃ -Ph | |
| | 89 | C-Me | 3-pyridyl | 2,4,6-Me ₃ -Ph | |
| | 90 | C-Me | CH(Et)CH ₂ CONMe ₂ | 2,4,6-Me ₃ -Ph | |
| 30 | 91 | C-Me | CH(Et)CH ₂ CH ₂ NMe ₂ | 2,4,6-Me ₃ -Ph | |
| | 92 ^P | C-Me | NHCH(CH ₂ OMe) ₂ | 2,4-Me ₂ -Ph | 44-45 |
| | 93 ^Q | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2,4-Me ₂ -Ph | oil |
| | 94 ^R | C-Me | NHCH(Et)CH ₂ OMe | 2,4-Me ₂ -Ph | 102-104 |
| | 95 ^S | C-Me | NH-3-pentyl | 2,4-Me ₂ -Ph | 102-104 |
| 35 | 96 ^T | C-Me | NEt ₂ | 2,4-Me ₂ -Ph | oil |
| | 97 ^U | C-Me | N(CH ₂ CN) ₂ | 2,4-Me ₂ -Ph | 148-150 |

| | | | | | |
|----|-------------------|------|---|--------------------------|---------|
| | 98 ^v | C-Me | NHCH (Me) CH ₂ OMe | 2, 4-Me ₂ -Ph | 102-104 |
| | 99 ^w | C-Me | OCH (Et) CH ₂ OMe | 2, 4-Me ₂ -Ph | oil |
| | 100 ^x | C-Me | NPr-c-C ₃ H ₅ | 2, 4-Me ₂ -Ph | oil |
| | 101 ^y | C-Me | NHCH (Me) CH ₂ NMe ₂ | 2, 4-Me ₂ -Ph | 47-48 |
| 5 | 102 ^z | C-Me | N (c-C ₃ H ₅) CH ₂ CH ₂ CN | 2, 4-Me ₂ -Ph | 117-118 |
| | 103 ^{aa} | C-Me | N (Pr) CH ₂ CH ₂ CN | 2, 4-Me ₂ -Ph | oil |
| | 104 ^{ab} | C-Me | N (Bu) CH ₂ CH ₂ CN | 2, 4-Me ₂ -Ph | oil |
| | 105 | C-Me | NHCHPr ₂ | 2, 4-Me ₂ -Ph | |
| | 106 | C-Me | NEtBu | 2, 4-Me ₂ -Ph | |
| 10 | 107 | C-Me | NPr (CH ₂ -c-C ₃ H ₅) | 2, 4-Me ₂ -Ph | |
| | 108 | C-Me | NH-3-heptyl | 2, 4-Me ₂ -Ph | |
| | 109 | C-Me | NEt ₂ | 2, 4-Me ₂ -Ph | |
| | 110 | C-Me | NHCH (CH ₂ OEt) ₂ | 2, 4-Me ₂ -Ph | |
| | 111 | C-Me | NH-3-pentyl | 2, 4-Me ₂ -Ph | |
| 15 | 112 | C-Me | NMePh | 2, 4-Me ₂ -Ph | |
| | 113 | C-Me | NPr ₂ | 2, 4-Me ₂ -Ph | |
| | 114 | C-Me | NH-3-hexyl | 2, 4-Me ₂ -Ph | |
| | 115 | C-Me | morpholino | 2, 4-Me ₂ -Ph | |
| | 116 | C-Me | N (CH ₂ Ph) CH ₂ CH ₂ OMe | 2, 4-Me ₂ -Ph | |
| 20 | 117 | C-Me | NHCH (CH ₂ Ph) CH ₂ OMe | 2, 4-Me ₂ -Ph | |
| | 118 | C-Me | NH-4-tetrahydropyranyl | 2, 4-Me ₂ -Ph | |
| | 119 | C-Me | NH-cyclopentyl | 2, 4-Me ₂ -Ph | |
| | 120 | C-Me | 1, 2, 3, 4-tetrahydro- isoquinolinyl | 2, 4-Me ₂ -Ph | |
| 25 | 121 | C-Me | CH ₂ -(1, 2, 3, 4-tetrahydro- isoquinolinyl) | 2, 4-Me ₂ -Ph | |
| | 122 | C-Me | OEt | 2, 4-Me ₂ -Ph | |
| | 123 | C-Me | OCH (Et) CH ₂ OMe | 2, 4-Me ₂ -Ph | |
| | 124 | C-Me | OCH ₂ Ph | 2, 4-Me ₂ -Ph | |
| 30 | 125 | C-Me | O-3-pentyl | 2, 4-Me ₂ -Ph | |
| | 126 | C-Me | SEt | 2, 4-Me ₂ -Ph | |
| | 127 | C-Me | S (O) Et | 2, 4-Me ₂ -Ph | |
| | 128 | C-Me | SO ₂ Et | 2, 4-Me ₂ -Ph | |
| | 3 | C-Me | CH (CO ₂ Et) ₂ | 2, 4-Me ₂ -Ph | 50-52 |
| 35 | 129 | C-Me | C (Et) (CO ₂ Et) ₂ | 2, 4-Me ₂ -Ph | |

| | | | | | |
|----|-------------------|------|--|-----------------------------|-------|
| | 130 | C-Me | CH(Et)CH ₂ OH | 2,4-Me ₂ -Ph | |
| | 131 | C-Me | CH(Et)CH ₂ OMe | 2,4-Me ₂ -Ph | |
| | 132 | C-Me | CH(Et)CH ₂ OEt | 2,4-Me ₂ -Ph | |
| | 133 | C-Me | CONMe ₂ | 2,4-Me ₂ -Ph | |
| 5 | 134 | C-Me | COCH ₃ | 2,4-Me ₂ -Ph | |
| | 135 | C-Me | CH(OH)CH ₃ | 2,4-Me ₂ -Ph | |
| | 136 | C-Me | C(OH)Ph-3-pyridyl | 2,4-Me ₂ -Ph | |
| | 137 | C-Me | Ph | 2,4-Me ₂ -Ph | |
| | 138 | C-Me | 2-CF ₃ -Ph | 2,4-Me ₂ -Ph | |
| 10 | 139 | C-Me | 2-Ph-Ph | 2,4-Me ₂ -Ph | |
| | 140 | C-Me | 3-pentyl | 2,4-Me ₂ -Ph | |
| | 141 | C-Me | cyclobutyl | 2,4-Me ₂ -Ph | |
| | 142 | C-Me | 3-pyridyl | 2,4-Me ₂ -Ph | |
| | 143 | C-Me | CH(Et)CH ₂ CONMe ₂ | 2,4-Me ₂ -Ph | |
| 15 | 144 | C-Me | CH(Et)CH ₂ CH ₂ NMe ₂ | 2,4-Me ₂ -Ph | |
| | 145 ^{bc} | C-Me | NHCH(CH ₂ OMe) ₂ | 2-Me-4-MeO-Ph | 45-46 |
| | 146 ^{bd} | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Me-4-MeO-Ph | oil |
| | 147 ^{be} | C-Me | NHCH(Et)CH ₂ OMe | 2-Me-4-MeO-Ph | 86-88 |
| | 148 ^{bf} | C-Me | N(Pr)CH ₂ CH ₂ CN | 2-Me-4-MeO-Ph | oil |
| 20 | 149 | C-Me | OCH(Et)CH ₂ OMe | 2-Me-4-MeO-Ph | |
| | 150 ^{af} | C-Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4-MeO-Ph | 88-90 |
| | 151 ^{al} | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Br-4-MeO-Ph | oil |
| | 152 ^{ag} | C-Me | NHCH(Et)CH ₂ OMe | 2-Br-4-MeO-Ph | 95-97 |
| | 153 | C-Me | N(Pr)CH ₂ CH ₂ CN | 2-Br-4-MeO-Ph | |
| 25 | 154 | C-Me | OCH(Et)CH ₂ OMe | 2-Br-4-MeO-Ph | |
| | 155 | C-Me | NHCH(CH ₂ OMe) ₂ | 2-Me-4-NMe ₂ -Ph | |
| | 156 | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Me-4-NMe ₂ -Ph | oil |
| | 157 | C-Me | NHCH(Et)CH ₂ OMe | 2-Me-4-NMe ₂ -Ph | |
| | 158 | C-Me | N(Pr)CH ₂ CH ₂ CN | 2-Me-4-NMe ₂ -Ph | |
| 30 | 159 | C-Me | OCH(Et)CH ₂ OMe | 2-Me-4-NMe ₂ -Ph | |
| | 160 | C-Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4-NMe ₂ -Ph | |
| | 161 | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Br-4-NMe ₂ -Ph | |
| | 162 | C-Me | NHCH(Et)CH ₂ OMe | 2-Br-4-NMe ₂ -Ph | |
| | 163 | C-Me | N(Pr)CH ₂ CH ₂ CN | 2-Br-4-NMe ₂ -Ph | |
| 35 | 164 | C-Me | OCH(Et)CH ₂ OMe | 2-Br-4-NMe ₂ -Ph | |
| | 165 | C-Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4-i-Pr-Ph | |

| | | | | | |
|----|-------------------|------|--------------------|-----------------------------------|---------|
| | 166 | C-Me | $N(CH_2CH_2OMe)_2$ | 2-Br-4-i-Pr-Ph | |
| | 167 | C-Me | $NHCH(Et)CH_2OMe$ | 2-Br-4-i-Pr-Ph | |
| | 168 | C-Me | $N(Pr)CH_2CH_2CN$ | 2-Br-4-i-Pr-Ph | |
| | 169 | C-Me | $OCH(Et)CH_2OMe$ | 2-Br-4-i-Pr-Ph | |
| 5 | 170 | C-Me | $NHCH(CH_2OMe)_2$ | 2-Br-4-Me-Ph | |
| | 171 | C-Me | $N(CH_2CH_2OMe)_2$ | 2-Br-4-Me-Ph | |
| | 172 | C-Me | $NHCH(Et)CH_2OMe$ | 2-Br-4-Me-Ph | |
| | 173 | C-Me | $N(Pr)CH_2CH_2CN$ | 2-Br-4-Me-Ph | |
| | 174 | C-Me | $OCH(Et)CH_2OMe$ | 2-Br-4-Me-Ph | |
| 10 | 175 ^{ar} | C-Me | $NHCH(CH_2OMe)_2$ | 2-Me-4-Br-Ph | 108-109 |
| | 176 | C-Me | $N(CH_2CH_2OMe)_2$ | 2-Me-4-Br-Ph | |
| | 177 | C-Me | $NHCH(Et)CH_2OMe$ | 2-Me-4-Br-Ph | |
| | 178 | C-Me | $N(Pr)CH_2CH_2CN$ | 2-Me-4-Br-Ph | |
| | 179 | C-Me | $OCH(Et)CH_2OMe$ | 2-Me-4-Br-Ph | |
| 15 | 180 | C-Me | $NHCH(CH_2OMe)_2$ | 2-Cl-4,6-Me ₂ -Ph | |
| | 181 | C-Me | $N(CH_2CH_2OMe)_2$ | 2-Cl-4,6-Me ₂ -Ph | |
| | 182 | C-Me | $NHCH(CH_2OMe)_2$ | 4-Br-2,6-(Me) ₂ -Ph | |
| | 183 | C-Me | $N(CH_2CH_2OMe)_2$ | 4-Br-2,6-(Me) ₂ -Ph | |
| | 184 | C-Me | $NHCH(CH_2OMe)_2$ | 4-i-Pr-2-SMe-Ph | |
| 20 | 185 | C-Me | $N(CH_2CH_2OMe)_2$ | 4-i-Pr-2-SMe-Ph | |
| | 186 | C-Me | $NHCH(CH_2OMe)_2$ | 2-Br-4-CF ₃ -Ph | |
| | 187 | C-Me | $N(CH_2CH_2OMe)_2$ | 2-Br-4-CF ₃ -Ph | |
| | 188 | C-Me | $NHCH(CH_2OMe)_2$ | 2-Br-4,6-(MeO) ₂ -Ph | |
| | 189 | C-Me | $N(CH_2CH_2OMe)_2$ | 2-Br-4,6-(MeO) ₂ -Ph | |
| 25 | 190 | C-Me | $NHCH(CH_2OMe)_2$ | 2-Cl-4,6-(MeO) ₂ -Ph | |
| | 191 | C-Me | $N(CH_2CH_2OMe)_2$ | 2-Cl-4,6-(MeO) ₂ -Ph | |
| | 192 | C-Me | $NHCH(CH_2OMe)_2$ | 2,6-(Me) ₂ -4-SMe-Ph | |
| | 193 | C-Me | $N(CH_2CH_2OMe)_2$ | 2,6-(Me) ₂ -4-SMe-Ph | |
| | 194 | C-Me | $NHCH(CH_2OMe)_2$ | 4-(COMe)-2-Br-Ph | |
| 30 | 195 | C-Me | $N(CH_2CH_2OMe)_2$ | 4-(COMe)-2-Br-Ph | |
| | 196 | C-Me | $NHCH(CH_2OMe)_2$ | 2,4,6-Me ₃ -pyrid-3-yl | |
| | 197 | C-Me | $N(CH_2CH_2OMe)_2$ | 2,4,6-Me ₃ -pyrid-3-yl | |
| | 198 | C-Me | $NHCH(CH_2OMe)_2$ | 2,4-(Br) ₂ -Ph | |
| | 199 | C-Me | $N(CH_2CH_2OMe)_2$ | 2,4-(Br) ₂ -Ph | |
| 35 | 200 | C-Me | $NHCH(CH_2OMe)_2$ | 4-i-Pr-2-SMe-Ph | |
| | 201 | C-Me | $N(CH_2CH_2OMe)_2$ | 4-i-Pr-2-SMe-Ph | |

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| | 202 | C-Me | NHCH (CH ₂ OMe) ₂ | 4-i-Pr-2-SO ₂ Me-Ph |
| | 203 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 4-i-Pr-2-SO ₂ Me-Ph |
| | 204 | C-Me | NHCH (CH ₂ OMe) ₂ | 2,6-(Me) ₂ -4-SMe-Ph |
| | 205 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2,6-(Me) ₂ -4-SMe-Ph |
| 5 | 206 | C-Me | NHCH (CH ₂ OMe) ₂ | 2,6-(Me) ₂ -4-SO ₂ Me-Ph |
| | 207 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2,6-(Me) ₂ -4-SO ₂ Me-Ph |
| | 208 | C-Me | NHCH (CH ₂ OMe) ₂ | 2-I-4-i-Pr-Ph |
| | 209 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2-I-4-i-Pr-Ph |
| | 210 | C-Me | NHCH (CH ₂ OMe) ₂ | 2-Br-4-N (Me) ₂ -6-MeO-Ph |
| 10 | 211 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2-Br-4-N (Me) ₂ -6-MeO-Ph |
| | 212 | C-Me | NHCH (CH ₂ OMe) ₂ | 2,4-[SMe] ₂ -Ph |
| | 213 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2,4-[SMe] ₂ -Ph |
| | 214 | C-Me | NHCH (CH ₂ OMe) ₂ | 2,4-[SO ₂ Me] ₂ -Ph |
| | 215 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2,4-[SO ₂ Me] ₂ -Ph |
| 15 | 216 | C-Me | NHCH (CH ₂ OMe) ₂ | 4-i-Pr-2-SMe-Ph |
| | 217 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 4-i-Pr-2-SMe-Ph |
| | 218 | C-Me | NHCH (CH ₂ OMe) ₂ | 4-i-Pr-2-SO ₂ Me-Ph |
| | 219 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 4-i-Pr-2-SO ₂ Me-Ph |
| | 220 | C-Me | NHCH (CH ₂ OMe) ₂ | 2-N (Me) ₂ -4-Me-Ph |
| 20 | 221 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2-N (Me) ₂ -4-Me-Ph |
| | 222 | C-Me | NHCH (CH ₂ OMe) ₂ | 2-MeS-4,6-(Me) ₂ -Ph |
| | 223 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2-MeS-4,6-(Me) ₂ -Ph |
| | 224 | C-Me | NHCH (CH ₂ OMe) ₂ | 2-(CH ₃ CO)-4,6-(Me) ₂ -Ph |
| | 225 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2-(CH ₃ CO)-4,6-(Me) ₂ -Ph |
| 25 | 226 | H | NHCH (CH ₂ OMe) ₂ | 2,4-Me ₂ -Ph |
| | 227 | H | NHCH (CH ₂ OMe) ₂ | 2,4-Me ₂ -Ph |
| | 228 | CF ₃ | N (CH ₂ CH ₂ OMe) ₂ | 2,4-Me ₂ -Ph |
| | 229 | CF ₃ | N (CH ₂ CH ₂ OMe) ₂ | 2,4-Me ₂ -Ph |
| | 230 | N | NHCH (CH ₂ OMe) ₂ | 2,4,6-Me ₃ -Ph |
| 30 | 231 | N | NHCHPr ₂ | 2,4,6-Me ₃ -Ph |
| | 232 | N | NEtBu | 2,4,6-Me ₃ -Ph |
| | 233 | N | NPr (CH ₂ -c-C ₃ H ₅) | 2,4,6-Me ₃ -Ph |
| | 234 | N | N (CH ₂ CH ₂ OMe) ₂ | 2,4,6-Me ₃ -Ph |
| | 235 | N | NH-3-heptyl | 2,4,6-Me ₃ -Ph |
| 35 | 236 | N | NHCH (Et) CH ₂ OMe | 2,4,6-Me ₃ -Ph |
| | 237 | N | NEt ₂ | 2,4,6-Me ₃ -Ph |

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| | 238 | N | NHCH(CH ₂ OEt) ₂ | 2,4,6-Me ₃ -Ph |
| | 239 | N | NH-3-pentyl | 2,4,6-Me ₃ -Ph |
| | 240 | N | NMePh | 2,4,6-Me ₃ -Ph |
| | 241 | N | NPr ₂ | 2,4,6-Me ₃ -Ph |
| 5 | 242 | N | NH-3-hexyl | 2,4,6-Me ₃ -Ph |
| | 243 | N | morpholino | 2,4,6-Me ₃ -Ph |
| | 244 | N | N(CH ₂ Ph)CH ₂ CH ₂ OMe | 2,4,6-Me ₃ -Ph |
| | 245 | N | NHCH(CH ₂ Ph)CH ₂ OMe | 2,4,6-Me ₃ -Ph |
| | 246 | N | NH-4-tetrahydropyranyl | 2,4,6-Me ₃ -Ph |
| 10 | 247 | N | NH-cyclopentyl | 2,4,6-Me ₃ -Ph |
| | 248 | N | 1,2,3,4-tetrahydro- isoquinolinyl | 2,4,6-Me ₃ -Ph |
| | 249 | N | CH ₂ -(1,2,3,4-tetrahydro- isoquinolinyl) | 2,4,6-Me ₃ -Ph |
| 15 | 250 | N | OEt | 2,4,6-Me ₃ -Ph |
| | 251 | N | OCH(Et)CH ₂ OMe | 2,4,6-Me ₃ -Ph |
| | 252 | N | OCH ₂ Ph | 2,4,6-Me ₃ -Ph |
| | 253 | N | O-3-pentyl | 2,4,6-Me ₃ -Ph |
| | 254 | N | SEt | 2,4,6-Me ₃ -Ph |
| 20 | 255 | N | S(O)Et | 2,4,6-Me ₃ -Ph |
| | 256 | N | SO ₂ Et | 2,4,6-Me ₃ -Ph |
| | 257 | N | CH(CO ₂ Et) ₂ | 2,4,6-Me ₃ -Ph |
| | 258 | N | C(Et)(CO ₂ Et) ₂ | 2,4,6-Me ₃ -Ph |
| | 259 | N | CH(Et)CH ₂ OH | 2,4,6-Me ₃ -Ph |
| 25 | 260 | N | CH(Et)CH ₂ OMe | 2,4,6-Me ₃ -Ph |
| | 261 | N | CONMe ₂ | 2,4,6-Me ₃ -Ph |
| | 262 | N | COCH ₃ | 2,4,6-Me ₃ -Ph |
| | 263 | N | CH(OH)CH ₃ | 2,4,6-Me ₃ -Ph |
| | 264 | N | C(OH)Ph-3-pyridyl | 2,4,6-Me ₃ -Ph |
| 30 | 265 | N | Ph | 2,4,6-Me ₃ -Ph |
| | 266 | N | 2-CF ₃ -Ph | 2,4,6-Me ₃ -Ph |
| | 267 | N | 2-Ph-Ph | 2,4,6-Me ₃ -Ph |
| | 268 | N | 3-pentyl | 2,4,6-Me ₃ -Ph |
| | 269 | N | cyclobutyl | 2,4,6-Me ₃ -Ph |
| 35 | 270 | N | 3-pyridyl | 2,4,6-Me ₃ -Ph |
| | 271 | N | CH(Et)CH ₂ CONMe ₂ | 2,4,6-Me ₃ -Ph |

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| | 272 | N | CH (Et) CH ₂ CH ₂ NMe ₂ | 2, 4, 6-Me ₃ -Ph |
| | 273 | N | NHCH (CH ₂ OMe) ₂ | 2, 4-Me ₂ -Ph |
| | 274 | N | NHCHPr ₂ | 2, 4-Me ₂ -Ph |
| | 275 | N | NEtBu | 2, 4-Me ₂ -Ph |
| 5 | 276 | N | NPr (CH ₂ -c-C ₃ H ₅) | 2, 4-Me ₂ -Ph |
| | 277 | N | N (CH ₂ CH ₂ OMe) ₂ | 2, 4-Me ₂ -Ph |
| | 278 | N | NH-3-heptyl | 2, 4-Me ₂ -Ph |
| | 279 | N | NHCH (Et) CH ₂ OMe | 2, 4-Me ₂ -Ph |
| | 280 | N | NEt ₂ | 2, 4-Me ₂ -Ph |
| 10 | 281 | N | NHCH (CH ₂ OEt) ₂ | 2, 4-Me ₂ -Ph |
| | 282 | N | NH-3-pentyl | 2, 4-Me ₂ -Ph |
| | 283 | N | NMePh | 2, 4-Me ₂ -Ph |
| | 284 | N | NPr ₂ | 2, 4-Me ₂ -Ph |
| | 285 | N | NH-3-hexyl | 2, 4-Me ₂ -Ph |
| 15 | 286 | N | morpholino | 2, 4-Me ₂ -Ph |
| | 287 | N | / N (CH ₂ Ph) CH ₂ CH ₂ OMe | 2, 4-Me ₂ -Ph |
| | 288 | N | NHCH (CH ₂ Ph) CH ₂ OMe | 2, 4-Me ₂ -Ph |
| | 289 | N | NH-4-tetrahydropyranyl | 2, 4-Me ₂ -Ph |
| | 290 | N | NH-cyclopentyl | 2, 4-Me ₂ -Ph |
| 20 | 291 | N | 1, 2, 3, 4-tetrahydro- isoquinolinyl | 2, 4-Me ₂ -Ph |
| | 292 | N | CH ₂ -(1, 2, 3, 4-tetrahydro- isoquinolinyl) | 2, 4-Me ₂ -Ph |
| | 293 | N | OEt | 2, 4-Me ₂ -Ph |
| 25 | 294 | N | OCH (Et) CH ₂ OMe | 2, 4-Me ₂ -Ph |
| | 295 | N | OCH ₂ Ph | 2, 4-Me ₂ -Ph |
| | 296 | N | O-3-pentyl | 2, 4-Me ₂ -Ph |
| | 297 | N | SEt | 2, 4-Me ₂ -Ph |
| | 298 | N | S (O) Et | 2, 4-Me ₂ -Ph |
| 30 | 299 | N | SO ₂ Et | 2, 4-Me ₂ -Ph |
| | 300 | N | CH (CO ₂ Et) ₂ | 2, 4-Me ₂ -Ph |
| | 301 | N | C (Et) (CO ₂ Et) ₂ | 2, 4-Me ₂ -Ph |
| | 302 | N | CH (Et) CH ₂ OH | 2, 4-Me ₂ -Ph |
| | 303 | N | CH (Et) CH ₂ OMe | 2, 4-Me ₂ -Ph |
| 35 | 304 | N | CONMe ₂ | 2, 4-Me ₂ -Ph |
| | 305 | N | COCH ₃ | 2, 4-Me ₂ -Ph |

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| | 306 | N | CH(OH)CH ₃ | 2,4-Me ₂ -Ph | |
| | 307 | N | C(OH)Ph-3-pyridyl | 2,4-Me ₂ -Ph | |
| | 308 | N | Ph | 2,4-Me ₂ -Ph | |
| | 309 | N | 2-CF ₃ -Ph | 2,4-Me ₂ -Ph | |
| 5 | 310 | N | 2-Ph-Ph | 2,4-Me ₂ -Ph | |
| | 311 | N | 3-pentyl | 2,4-Me ₂ -Ph | |
| | 312 | N | cyclobutyl | 2,4-Me ₂ -Ph | |
| | 313 | N | 3-pyridyl | 2,4-Me ₂ -Ph | |
| | 314 | N | CH(Et)CH ₂ CONMe ₂ | 2,4-Me ₂ -Ph | |
| 10 | 315 | N | CH(Et)CH ₂ CH ₂ NMe ₂ | 2,4-Me ₂ -Ph | |
| | 316an | C-Me | NEt ₂ | 2-Br-4-MeO-Ph | oil |
| | 317am | C-Me | NH-3-pentyl | 2-Br-4-MeO-Ph | oil |
| | 318aj | C-Me | NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe | 2,4,6-Me ₃ -Ph | 101-103 |
| | 319ao | C-Me | NH(c-C ₃ H ₅) | 2,4-Me ₂ -Ph | oil |
| 15 | 320ak | C-Me | morpholino | 2,4,6-Me ₃ -Ph | 139-141 |
| | 321ap | C-Me | NHCH(CH ₂ OMe) ₂ | 2-CN-4-Me-Ph | 152-153 |
| | 322aq | C-Me | N(c-C ₃ H ₅)CH ₂ CH ₂ CN | 2,4,6-Me ₃ -Ph | 149-151 |
| | 324as | C-Me | NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe | 2-Me-4-Br-Ph | 115-117 |
| | 325at | C-Me | NHCH(CH ₂ OMe) ₂ | 2,5-Me ₂ -4-MeO-Ph | 55-57 |
| 20 | 326au | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2,5-Me ₂ -4-MeO-Ph | 72 |
| | 327av | C-Me | NH-3-pentyl | 2,5-Me ₂ -4-MeO-Ph | 45-47 |
| | 328aw | C-Me | NEt ₂ | 2,5-Me ₂ -4-MeO-Ph | oil |
| | 329ax | C-Me | NHCH(CH ₂ OMe) ₂ | 2-Cl-4-MePh | 80-81 |
| | 330ay | C-Me | NCH(Et)CH ₂ OMe | 2-Cl-4-MePh | 77-79 |
| 25 | 331az | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Cl-4-MePh | oil |
| | 332ba | C-Me | (S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe | 2-Cl-4-MePh | 139-140 |
| | 333bb | C-Me | N(c-C ₃ H ₅)CH ₂ CH ₂ CN | 2,5-Me ₂ -4-MeOPh | 120-122 |
| | 334bg | C-Me | NEt ₂ | 2-Me-4-MeOPh | oil |
| | 335bh | C-Me | OEt | 2-Me-4-MeOPh | oil |
| 30 | 336bi | C-Me | (S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe | 2-Me-4-MeOPh | oil |
| | 337bj | C-Me | N(c-C ₃ H ₅)CH ₂ CH ₂ CN | 2-Me-4-MeOPh | 129 |
| | 338bk | C-Me | NHCH(CH ₂ CH ₂ OEt) ₂ | 2-Me-4-MeOPh | amorph. |
| | 339 | C-Me | N(c-C ₃ H ₅)CH ₂ CH ₂ CN | 2,4-Cl ₂ -Ph | 109-110 |
| | 340 | C-Me | (S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe | 2,4-Cl ₂ -Ph | 93-94 |
| 35 | 341 | C-Me | NH-3-pentyl | 2-Me-4-BrPh | 118-119 |
| | 342 | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Me-4-BrPh | oil |

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| | 343 | C-Me | NHCH(CH ₂ -iPr)CH ₂ OMe | 2,4-Me ₂ -Ph | oil |
| | 344 | C-Me | NHCH(Pr)CH ₂ OMe | 2,4-Me ₂ -Ph | 94-95 |
| | 345 | C-Me | NHCH(Et)CH ₂ OEt | 2,4-Me ₂ -Ph | 76-77 |
| | 346 | C-Me | NHCH(CH ₂ OMe)CH ₂ CH ₂ OMe | 2-Me-4-Me ₂ NPh | oil |
| 5 | 347 | C-Me | NEt ₂ | 2-Me-4-ClPh | oil |
| | 348 | C-Me | NH-3-pentyl | 2-Me-4-ClPh | 122-124 |
| | 349 | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Me-4-ClPh | oil |
| | 350 | C-Me | NHCH(CH ₂ OMe) ₂ | 2-Me-4-ClPh | 122-123 |
| | 351 | C-Me | NEt ₂ | 2-Me-4-ClPh | oil |
| 10 | 352 | C-Me | NEt ₂ | 2-Cl-4-MePh | oil |
| | 353 | C-Me | NH-3-pentyl | 2-Cl-4-MePh | 120-121 |
| | 354 | C-Me | NHCH(CH ₂ OMe) ₂ | 2-Cl-4-MeOPh | |
| | 355 ^{bl} | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Cl-4-MeOPh | oil |
| | 356 ^{bm} | C-Me | NHCH(Et)CH ₂ OMe | 2-Cl-4-MeOPh | 108-110 |
| 15 | 357 ^{bn} | C-Me | N(c-Pr)CH ₂ CH ₂ CN | 2-Cl-4-MeOPh | 127-129 |
| | 358 ^{bo} | C-Me | NEt ₂ | 2-Cl-4-MeOPh | oil |
| | 359 ^{bp} | C-Me | NH-3-pentyl | 2-Cl-4-MeOPh | 77-79 |
| | 360 | C-Me | NHCH(Et)CH ₂ CH ₂ OMe | 2-Cl-4-MeOPh | |
| | 361 | C-Me | NHCH(Me)CH ₂ CH ₂ OMe | 2-Cl-4-MeOPh | |
| 20 | 362 | C-Me | NHCH(Et)CH ₂ CH ₂ OMe | 2-Br-4-MeOPh | |
| | 363 | C-Me | NHCH(Me)CH ₂ CH ₂ OMe | 2-Br-4-MeOPh | |
| | 364 | C-Me | NHCH(Et)CH ₂ CH ₂ OMe | 2-Me-4-MeOPh | |
| | 365 | C-Me | NHCH(Me)CH ₂ CH ₂ OMe | 2-Me-4-MeOPh | |
| | 366 | C-Me | NHCH(CH ₂ OMe) ₂ | 2-Cl-4,5-(MeO) ₂ Ph | |
| 25 | 367 | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Cl-4,5-(MeO) ₂ Ph | |
| | 368 | C-Me | NHCH(Et)CH ₂ OMe | 2-Cl-4,5-(MeO) ₂ Ph | |
| | 369 | C-Me | N(c-Pr)CH ₂ CH ₂ CN | 2-Cl-4,5-(MeO) ₂ Ph | |
| | 370 | C-Me | NEt ₂ | 2-Cl-4,5-(MeO) ₂ Ph | |
| | 371 | C-Me | NH-3-pentyl | 2-Cl-4,5-(MeO) ₂ Ph | |
| 30 | 372 | C-Me | NHCH(Et)CH ₂ CH ₂ OMe | 2-Cl-4,5-(MeO) ₂ Ph | |
| | 373 | C-Me | NHCH(Me)CH ₂ CH ₂ OMe | 2-Cl-4,5-(MeO) ₂ Ph | |
| | 374 ^{bq} | C-Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4,5-(MeO) ₂ Ph | 137-138 |
| | 375 | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Br-4,5-(MeO) ₂ Ph | |
| | 376 ^{br} | C-Me | NHCH(Et)CH ₂ OMe | 2-Br-4,5-(MeO) ₂ Ph | 147-148 |
| 35 | 377 | C-Me | N(c-Pr)CH ₂ CH ₂ CN | 2-Br-4,5-(MeO) ₂ Ph | |
| | 378 ^{bs} | C-Me | NEt ₂ | 2-Br-4,5-(MeO) ₂ Ph | 52-58 |

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| | 379 | C-Me | NH-3-pentyl | 2-Br-4, 5- (MeO) ₂ Ph |
| | 380 | C-Me | NHCH (Et) CH ₂ CH ₂ OMe | 2-Br-4, 5- (MeO) ₂ Ph |
| | 381 | C-Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-Br-4, 5- (MeO) ₂ Ph |
| | 382 | C-Me | NHCH (CH ₂ OMe) ₂ | 2-Cl-4, 6- (MeO) ₂ Ph |
| 5 | 383 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2-Cl-4, 6- (MeO) ₂ Ph |
| | 384 | C-Me | NHCH (Et) CH ₂ OMe | 2-Cl-4, 6- (MeO) ₂ Ph |
| | 385 | C-Me | N (c-Pr) CH ₂ CH ₂ CN | 2-Cl-4, 6- (MeO) ₂ Ph |
| | 386 | C-Me | NEt ₂ | 2-Cl-4, 6- (MeO) ₂ Ph |
| | 387 | C-Me | NH-3-pentyl | 2-Cl-4, 6- (MeO) ₂ Ph |
| 10 | 388 | C-Me | NHCH (Et) CH ₂ CH ₂ OMe | 2-Cl-4, 6- (MeO) ₂ Ph |
| | 389 | C-Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-Cl-4, 6- (MeO) ₂ Ph |
| | 390 | C-Me | NHCH (CH ₂ OMe) ₂ | 2-Me-4, 6- (MeO) ₂ Ph |
| | 391 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2-Me-4, 6- (MeO) ₂ Ph |
| | 392 | C-Me | NHCH (Et) CH ₂ OMe | 2-Me-4, 6- (MeO) ₂ Ph |
| 15 | 393 | C-Me | N (c-Pr) CH ₂ CH ₂ CN | 2-Me-4, 6- (MeO) ₂ Ph |
| | 395 | C-Me | NEt ₂ | 2-Me-4, 6- (MeO) ₂ Ph |
| | 396 | C-Me | NH-3-pentyl | 2-Me-4, 6- (MeO) ₂ Ph |
| | 397 | C-Me | NHCH (Et) CH ₂ CH ₂ OMe | 2-Me-4, 6- (MeO) ₂ Ph |
| | 398 | C-Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-Me-4, 6- (MeO) ₂ Ph |
| 20 | 399 | C-Me | N (c-Pr) CH ₂ CH ₂ CN | 2-Br-4, 6- (MeO) ₂ Ph |
| | 400 | C-Me | NEt ₂ | 2-Br-4, 6- (MeO) ₂ Ph |
| | 401 | C-Me | NH-3-pentyl | 2-Br-4, 6- (MeO) ₂ Ph |
| | 402 | C-Me | NHCH (Et) CH ₂ CH ₂ OMe | 2-Br-4, 6- (MeO) ₂ Ph |
| | 403 | C-Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-Br-4, 6- (MeO) ₂ Ph |
| 25 | 404 | C-Me | NHCH (Et) CH ₂ CH ₂ OMe | 2-Me-4-MeOPh |
| | 405 | C-Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-Me-4-MeOPh |
| | 406 | C-Me | NHCH (CH ₂ OMe) ₂ | 2-MeO-4-MePh |
| | 407 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2-MeO-4-MePh |
| | 408 | C-Me | NHCH (Et) CH ₂ OMe | 2-MeO-4-MePh |
| 30 | 409 | C-Me | N (c-Pr) CH ₂ CH ₂ CN | 2-MeO-4-MePh |
| | 410 | C-Me | NEt ₂ | 2-MeO-4-MePh |
| | 411 | C-Me | NH-3-pentyl | 2-MeO-4-MePh |
| | 412 | C-Me | NHCH (Et) CH ₂ CH ₂ OMe | 2-MeO-4-MePh |
| | 413 | C-Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-MeO-4-MePh |
| 35 | 414 | C-Me | NHCH (CH ₂ OMe) ₂ | 2-MeO-4-MePh |
| | 415 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2-MeO-4-MePh |

| | | | | | |
|----|-------------------|------|---|--------------|-----|
| | 416 | C-Me | NHCH(Et)CH ₂ OMe | 2-MeO-4-MePh | |
| | 417 | C-Me | N(c-Pr)CH ₂ CH ₂ CN | 2-MeO-4-MePh | |
| | 418 | C-Me | NEt ₂ | 2-MeO-4-MePh | |
| | 419 | C-Me | NH-3-pentyl | 2-MeO-4-MePh | |
| 5 | 420 | C-Me | NHCH(Et)CH ₂ CH ₂ OMe | 2-MeO-4-MePh | |
| | 421 | C-Me | NHCH(Me)CH ₂ CH ₂ OMe | 2-MeO-4-MePh | |
| | 423 ^{bt} | C-Me | NHCH(CH ₂ OMe) ₂ | 2-MeO-4-ClPh | oil |
| | 424 | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-MeO-4-ClPh | |
| | 425 | C-Me | NHCH(Et)CH ₂ OMe | 2-MeO-4-ClPh | |
| 10 | 426 | C-Me | N(c-Pr)CH ₂ CH ₂ CN | 2-MeO-4-ClPh | |
| | 427 | C-Me | NEt ₂ | 2-MeO-4-ClPh | |
| | 428 | C-Me | NH-3-pentyl | 2-MeO-4-ClPh | |
| | 429 | C-Me | NHCH(Et)CH ₂ CH ₂ OMe | 2-MeO-4-ClPh | |
| | 430 | C-Me | NHCH(Me)CH ₂ CH ₂ OMe | 2-MeO-4-ClPh | |

15

NOTES FOR TABLE 1:

- a) Analysis Calcd: C, 52.69, H, 5.17, N, 17.07, Cl, 17.28; Found: C, 52.82, H, 5.06, N, 16.77, Cl, 17.50.
- 20 b) CI-HRMS: Calcd: 406.1565, Found: 405.1573 (M + H); Analysis Calcd: C: 59.11; H: 6.20; N: 17.23; Cl: 17.45; Found: C: 59.93; H: 6.34; N: 16.50; Cl: 16.95;
- 25 NMR (CDCl₃, 300 MHz): 0.95 (t, J = 8, 4H), 1.30-1.40 (m, 4H), 1.50-1.75 (m, 4H), 2.35 (s, 3H), 2.48 (s, 3H), 4.30-4.45 (m, 1H), 6.15 (d, J = 8, 1H), 7.30 (s, 2H), 7.50 (s, 1H)
- 30 c) CI-HRMS: Calcd: 392.1409, Found: 392.1388 (M + H); NMR (CDCl₃, 300 MHz): 1.00 (t, J = 8, 3H), 1.35 (t, J = 8, 3H), 1.41 (q, J = 8, 2H), 1.65-1.85 (m, 2H), 2.30 (s, 3H), 2.40 (s, 3H), 3.85-4.20 (m, 4H), 7.30 (s, 2H), 7.50 (s, 1H).
- 35 d) CI-HRMS: Calcd: 404.1409, Found: 404.1408 (M + H); NMR(CDCl₃, 300 MHz): 0.35-0.45 (m, 2H), 0.52-0.62 (m, 2H), 0.98 (t, J = 8, 3H), 1.70-1.90 (m, 2H),

- 2.30 (s, 3H), 2.40 (s, 3H), 3.85-4.02 (m, 2H),
4.02-4.20 (m, 2H), 7.30 (s, 2H), 7.50 (s, 1H).
- 5 e) CI-HRMS: Calcd: 424.1307, Found: 424.1307 (M + H);
NMR (CDCl₃, 300 MHz): 2.28 (s, 3H), 2.40 (s, 3H),
3.40 (s, 6H), 3.75 (t, J = 8, 4H), 4.20-4.45 (m,
4H), 7.30 (s, 2H), 7.50 (s, 1H).
- 10 f) CI-HRMS: Calcd: 406.1565, Found: 406.1578 (M + H);
NMR (CDCl₃, 300 MHz): 0.90 (t, J = 8, 3H), 1.00 (t,
J = 8, 3H), 1.28-1.45 (m, 4H), 1.50-1.80 (m, 4H),
2.35 (s, 3H), 2.50 (s, 3H), 4.20-4.35 (m, 1H),
6.10-6.23 (m, 1H), 7.30 (s, 2H), 7.50 (s, 1H).
- 15 g) CI-HRMS: Calcd: 394.1201, Found: 394.1209 (M + H);
NMR (CDCl₃, 300 MHz): 1.02 (t, J = 8, 3H), 1.65-
1.90 (m, 2H), 2.35 (s, 3H), 2.48 (s, 3H), 3.40 (s,
3H), 3.50-3.60 (m, 2H), 4.35-4.45 (brs, 1H), 6.50-
6.60 (m, 1H), 7.30 (s, 2H), 7.50 (s, 1H).
- 20 h) CI-HRMS: Calcd: 364.1096, Found: 364.1093 (M + H);
Analysis: Calcd: C: 56.05; H: 5.27; N: 19.23; Cl:
19.46; Found: C: 55.96; H: 5.24; N: 18.93; Cl:
19.25;
NMR (CDCl₃, 300 MHz): 1.35 (t, J = 8, 6H), 2.30 (s,
3H), 2.40 (s, 3H), 3.95-4.15 (m, 4H), 7.30 (s, 2H),
7.50 (d, J = 1, 1H).
- 25 i) CI-HRMS: Calcd: 438.1464, Found: 438.1454 (M + H);
NMR (CDCl₃, 300 MHz): 1.22 (t, J = 8, 6H), 2.35 (s,
3H), 2.47 (s, 3H), 3.39 (q, J = 8, 4H), 3.65 (dd, J
= 8, 1, 2H), 3.73 (dd, J = 8, 1, 2H), 4.55-4.65 (m,
1H), 6.75 (d, J = 8, 1H), 7.30 (d, J = 1, 2H), 7.50
(s, 1H).
- 30 j) CI-HRMS: Calcd: 378.1252, Found: 378.1249 (M + H);
Analysis: Calcd: C: 57.15; H: 5.61; N: 18.51; Cl:
18.74; Found: C: 57.56; H: 5.65; N: 18.35; Cl:
18.45;
NMR (CDCl₃, 300 MHz): 1.00 (t, J = 8, 6H), 1.55-
35 1.70 (m, 2H), 1.70-1.85 (m, 2H), 2.35 (s, 3H), 2.50

- (s, 3H), 4.15-4.25 (m, 1H), 6.18 (d, J = 8, 1H), 7.30 (s, 2H), 7.50 (s, 1H).
- 5 k) CI-HRMS: Calcd: 398.0939, Found: 398.0922 (M + H); Analysis: Calcd: C: 60.31; H: 4.30; N: 17.58; Cl: 17.80; Found: C: 60.29; H: 4.59; N: 17.09; Cl: 17.57; NMR (CDCl₃, 300 MHz): 2.05 (s, 3H), 2.50 (s, 3H), 3.78 (s, 3H), 7.20-7.45 (m, 7H), 7.50 (d, J = 1, 1H).
- 10 l) CI-HRMS: Calcd: 392.1409, Found: 392.1391 (M + H); NMR (CDCl₃, 300 MHz): 0.98 (t, J = 8, 6H), 1.70-1.85 (m, 4H), 2.30 (s, 3H), 2.40 (s, 3H), 3.80-4.10 (m, 4H), 7.30 (s, 2H), 7.50 (d, J = 1, 1H).
- 15 m) CI-HRMS: Calcd: 392.1409, Found: 392.1415 (M + H); Analysis: Calcd: C: 58.17; H: 5.92; N: 17.85; Cl: 18.07; Found: C: 58.41; H: 5.85; N: 18.10; Cl: 17.75; NMR (CDCl₃, 300 MHz): 0.90-1.05 (m, 6H), 1.35-1.55 (m, 2H), 1.55-1.85 (m, 4H), 2.35 (s, 3H), 2.48 (s, 3H), 4.20-4.35 (m, 1H), 6.15 (d, J = 8, 1H), 7.30 (s, 2H), 7.50 (d, J = 1, 1H).
- 20 n) CI-HRMS: Calcd: 337.0623, Found: 337.0689 (M + H); Analysis: Calcd: C: 53.43; H: 4.18; N: 16.62; Cl: 21.03, Found: C: 53.56; H: 4.33; N: 16.56; Cl: 20.75; NMR (CDCl₃, 300 MHz): 1.60 (t, J = 8, 3H), 2.40 (s, 3H), 2.55 (s, 3H), 4.80 (q, J = 8, 2H), 7.30 (d, J = 8, 1H), 7.35 (dd, J = 8, 1, 1H), 7.55 (d, J = 1, 1H).
- 25 o) CI-HRMS: Calcd: 383.2321, Found: 383.2309 (M + H); NMR (CDCl₃, 300 MHz): 2.00 (s, 6H), 2.20 (s, 3H), 2.30 (s, 3H), 2.45 (s, 3H), 3.45 (s, 6H), 3.61 (dd, J = 8, 8, 2H), 3.70 (dd, J = 8, 8, 2H), 4.60-4.70 (m, 1H), 6.70 (d, J = 8, 1H), 6.94 (s, 2H).
- 30 p) CI-HRMS: Calcd: 370.2243, Found: 370.2246 (M + H);
- 35

- Analysis: Calcd: C: 65.02; H: 7.38; N: 18.96;
Found: C: 65.22; H: 7.39; N: 18.71;
NMR (CDCl₃, 300 MHz): 2.18 (s, 3H), 2.30 (s, 3H),
2.45 (s, 3H), 3.45 (s, 6H), 3.60 (dd, J = 8, 8,
2H), 3.69 (dd, J = 8, 8, 2H), 4.60-4.70 (m, 1H),
6.70 (d, J = 8, 1H), 7.05 (d, J = 8, 1H), 7.07 (d,
J = 8, 1H), 7.10 (s, 1H).
- 5 q) CI-HRMS: Calcd: 384.2400, Found: 384.2393 (M + H);
NMR (CDCl₃, 300 MHz): 2.16 (s, 3H), 2.25 (s, 3H),
10 2.35 (s, 3H), 2.39 (s, 3H), 3.40 (s, 6H), 3.77 (t,
J = 8, 4H), 4.20-4.45 (m, 4H), 7.02 (d, J = 8, 1H)
7.05 (s, 1H), 7.10 (d, J = 7, 1H).
- r) CI-HRMS: Calcd: 354.2294, Found: 354.2271 (M + H);
Analysis: Calcd: C: 67.96; H: 7.71; N: 19.81;
15 Found: C: 67.56; H: 7.37; N: 19.60;
NMR (CDCl₃, 300 MHz): 1.03 (t, J = 8, 3H), 1.65-
1.88 (m, 2H), 2.17 (s, 3H), 2.30 (s, 3H), 2.35 (s,
3H), 2.45 (s, 3H), 3.40 (s, 3H), 3.50-3.62 (m, 2H),
20 4.30-4.45 (m, 1H), 6.51 (d, J = 8, 1H), 7.04 (d, J
= 8, 1H), 7.10 (d, J = 8, 1H), 7.12 (s, 1H).
- s) CI-HRMS: Calcd: 338.2345, Found: 338.2332 (M + H);
Analysis: Calcd: C: 71.18; H: 8.06; N: 20.75;
Found: C: 71.43; H: 7.80; N: 20.70;
25 NMR (CDCl₃, 300 MHz): 1.00 (t, J = 8, 6H), 1.55-
1.70 (m, 2H), 1.70-1.85 (m, 2H), 2.19 (s, 3H), 2.30
(s, 3H), 2.35 (s, 3H), 2.46 (s, 3H), 4.15-4.26 (m,
1H), 6.17 (d, J = 8, 1H), 7.06 (d, J = 8, 1H), 7.10
(d, J = 1, 1H), 7.13 (s, 1H).
- 30 t) CI-HRMS: Calcd: 324.2188, Found: 324.2188 (M + H);
NMR (CDCl₃, 300 MHz): 1.25 (t, J = 8, 6H), 2.16 (s,
3H), 2.28 (s, 3H), 2.35 (s, 3H), 2.40 (s, 3H),
3.95-4.20 (m, 4H), 7.05 (dd, J = 8, 1, 1H), 7.07
(s, 1H), 7.10 (d, J = 1, 1H)
- 35 u) CI-HRMS: Calcd: 346.1780, Found: 346.1785 (M + H);
Analysis: Calcd: C: 66.07; H: 5.54; N: 28.39;
Found: C: 66.07; H: 5.60; N: 27.81;

- NMR (CDCl₃, 300 MHz): 2.15 (s, 3H), 2.32 (s, 3H)
2.17 (s, 3H), 2.52 (s, 3H), 5.25-5.35 (m, 4H), 7.08
(s, 2H), 7.15 (s, 1H).
- 5 v) CI-HRMS: Calcd: 340.2137, Found: 340.2137 (M + H);
Analysis: Calcd: C: 67.23; H: 7.42; N: 20.63;
Found: C: 67.11; H: 7.39; N: 20.26;
NMR (CDCl₃, 300 MHz): 1.40 (d, J = 8, 3H), 2.16 (s,
3H), 2.32 (s, 3H), 2.35 (s, 3H), 2.47 (s, 3H), 3.42
(s, 3H), 3.50-3.60 (m, 2H), 4.50-4.15 (m, 1H), 6.56
10 (d, J = 8, 1H), 7.00-7.15 (m, 3H).
- w) CI-HRMS: Calcd: 355.2134, Found: 355.2134 (M + H);
NMR (CDCl₃, 300 MHz): 1.05 (t, J = 8, 3H), 1.85-
2.00 (m, 2H), 2.17 (s, 3H), 2.36 (s, 6H), 2.50 (s,
3H), 3.41 (s, 3H), 3.45 (dd, J = 8, 3, 1H), 3.82
15 (dd, J = 8, 1, 1H), 5.70-5.80 (m, 1H), 7.00-7.20
(m, 3H).
- x) CI-HRMS: Calcd: 364.2501, Found: 364.2501 (M + H);
NMR (CDCl₃, 300 MHz): 0.35-0.43 (m, 2H), 0.50-0.60
(m, 2H), 0.98 (t, J = 8, 3H), 1.20-1.30 (m, 1H),
20 1.72-1.90 (m, 2H), 2.18 (s, 3H) 2.28 (s, 3H), 2.35
(s, 3H), 2.40 (s, 3H), 3.88-4.03 (m, 2H), 4.03-4.20
(m, 2H), 7.00-7.15 (m, 3H).
- y) CI-HRMS: Calcd: 353.2454, Found: 353.2454 (M + H);
Analysis: Calcd: C: 68.15; H: 8.02; N: 23.84;
25 Found: C: 67.43; H: 7.81; N: 23.45;
NMR (CDCl₃, 300 MHz): 1.38 (d, J = 8, 3H), 2.18 (s,
3H), 2.30-2.40 (m, 12H), 2.47 93, 3H), 2.60-2.75
(m, 2H), 4.30-4.50 (m, 1H), 6.60-6.70 (m, 1H),
7.00-7.15 (m, 3H).
- 30 z) CI-HRMS: Calcd: 361.2140, Found: 361.2128 (M + H);
NMR (CDCl₃, 300 MHz): 0.75-0.83 (m, 2H), 1.00-1.10
(m, 2H), 2.17 (s, 3H), 2.30 (s, 3H), 2.36 (s, 3H),
2.47 (s, 3H), 2.85 (t, J = 8, 2H), 3.30-3.40 (m,
1H), 4.40-4.55 (m, 2H), 7.00-7.18 (m, 3H).
- 35 aa) CI-HRMS: Calcd: 363.2297, Found: 363.2311 (M + H);

- 5 NMR (CDCl₃, 300 MHz): 1.01 (t, 3H, J=8), 1.75-1.90 (m, 2H), 2.15 (s, 3H), 2.19 (s, 3H), 2.35 (s, 3H), 2.40 (s, 3H), 2.40 (s, 3H), 2.98 (t, 2H, J = 8), 3.97-4.15 (m, 2H), 4.15-4.30 (m, 2H), 7.03 (d, 1H, 1H), 7.08 (d, 1H, J = 8), 7.10 (s, 1H).
- 10 ab) CI-HRMS: Calcd: 363.2297, Found: 363.2295 (M + H); NMR (CDCl₃, 300 MHz): 1.01 (t, 3H, J = 8), 1.35-1.55 (m, 2H), 1.75-1.90 (m, 2H), 2.15 (s, 3H), 2.30 (s, 3H), 2.36 (s, 3H), 2.46 (s, 3H), 4.10-4.30 (m, 2H), 4.95-5.10 (br s, 2H), 7.05 (d, 1H, J = 8), 7.10 (d, 1H, J = 8), 7.15 (s, 1H).
- 15 ac) CI-HRMS: Calcd: 368.2450, Found: 368.2436; Analysis: Calcd: C, 68.62, H, 7.95, N, 19.06; Found: C, 68.73, H, 7.97, N, 19.09; NMR (CDCl₃, 300 MHz): 1.05 (t, J = 8, 3H), 1.70-1.90 (m, 2H), 2.01 (d, J = 3, 6H), 2.20 (s, 3H), 2.30 (s, 3H), 2.46, 2.465 (s, s, 3H), 3.42, 3.48 (s, s, 3H), 3.53-3.63 (m, 2H), 4.35-4.45 (m, 1H), 6.73 (d, J = 8, 1H), 6.97 (s, 2H).
- 20 (ad) CI- HRMS: Calcd: 352.2501, Found: 352.2500 (M + H): Analysis: Calcd: C: 71.76; H: 8.33; N: 19.92, Found: C: 71.55; H: 8.15; N: 19.28; NMR (CDCl₃, 300 MHz): 1.01 (t, J = 8, 6H), 1.58 -1.70 (m, 2H), 1.70-1.85 (m, 2H), 2.02 (s, 6H), 2.19 (s, 3H), 2.45 (s, 3H), 4.12-4.28 (m, 1H), 6.18 (d, J = 8, 1H), 6.95 (s, 2H).
- 25 (ae) CI- HRMS: Calcd: 398.2556, Found: 398.2551 (M + H); Analysis: Calcd: C: 66.47; H: 7.86; N: 17.62, Found: C: 66.74; H: 7.79; N: 17.70; NMR (CDCl₃, 300 MHz): 2.00 (s, 6H), 2.12 (s, 3H), 2.30 (s, 3H), 2.37 (s, 3H), 3.40 (s, 6H), 3.78 (t, J = 8, 4H), 4.25-4.40 (m, 4H), 6.93 (s, 2H).
- 30 (af) CI-HRMS: Calcd: 450.1141, Found: 450.1133 (M + H); Analysis: Calcd: C: 50.67; H: 5.37; N: 15.55; Br: 17.74; Found: C: 52.36; H: 5.84; N: 14.90; Br: 17.44;
- 35

- 5 NMR (CDCl₃, 300 MHz): 2.32 (s, 3H), 2.57 (s, 3H),
3.42 (s, 6H), 3.60 (q, J = 8, 2H), 3.69 (q, J = 8,
2H), 3.82 (s, 3H), 4.60-4.70 (m, 1H), 6.73 (d, J =
8, 1H), 6.93 (dd, J = 8, 1, 1H), 7.22 (d, J = 8,
1H).
- ag) CI-HRMS: Calcd: 434.1192, Found: 434.1169 (M + H);
Analysis: Calcd: C: 52.54; H: 5.58; N: 16.12; Br:
18.40; Found: C: 52.57; H: 5.60; N: 15.98; Br:
18.22;
- 10 NMR (CDCl₃, 300 MHz): 1.00-1.07 (m, 3H), 1.65-1.85
(m, 2H), 2.35 (s, 3H), 2.46, 2.47 (s, s, 3H), 3.40,
3.45 (s, s, 3H), 3.83 (s, 3H), 4.35-4.45 (m, 1H),
6.55 (d, J = 8, 1H), 6.92 (dd, J = 8, 1, 1H), 7.20-
7.30 (m, 2H).
- 15 ah) CI-HRMS: Calcd: 337.2266, Found: 337.2251 (M + H);
Analysis: Calcd: C: 70.18; H: 8.06; N: 20.75;
Found: C: 70.69; H: 7.66; N: 20.34;
NMR (CDCl₃, 300 MHz): 1.35 (t, J = 8, 6H), 2.01 (s,
6H), 2.15 (s, 3H), 2.30 (s, 3H), 2.38 (s, 3H), 4.07
20 (q, J = 8, 4H), 6.93 (s, 2H).
- ai) CI-HRMS: Calcd: 412.2713, Found: 412.2687 (M + H);
Analysis: Calcd: C: 67.13; H: 8.08; N: 17.02;
Found : C: 67.22; H: 7.85; N: 17.13;
NMR (CDCl₃, 300 MHz): 1.24 (t, J = 8, 6H), 2.00 (s,
25 6H), 2.20 (s, 3H), 2.30 (s, 3H), 2.43 (s, 3H), 3.60
(q, J = 8, 4H), 3.66 (dd, J = 8, 3, 2H), 3.75 (dd,
J = 8, 3, 2H), 4.55-4.65 (m, 1H), 6.75 (d, J = 8,
1H), 6.95 (s, 2H).
- aj) CI-HRMS: Calcd: 398.2556, Found: 398.2545 (M + H);
30 Analysis: Calcd: C: 66.47; H: 7.86; N: 17.62;
Found: C: 66.87; H: 7.62; N: 17.75;
NMR (CDCl₃, 300 MHz): 1.95-2.10 (m, 8H), 2.20 (s,
3H), 2.32 (s, 3H), 2.44 (s, 3H), 3.38 (s, 3H), 3.42
(s, 3H), 3.50-3.70 (m, 4H), 4.58-4.70 (m, 1H), 6.87
35 (d, J = 8, 1H), 6.95 (s, 2H).
- ak) CI-HRMS: Calcd: 338.1981, Found: 338.1971 (M + H);

- Analysis: Calcd: C: 67.63; H: 6.87; N: 20.06;
 Found: C: 67.67; H: 6.82; N: 20.31;
 NMR (CDCl₃, 300 MHz): 2.15 (s, 3H), 2.29 (s, 3H),
 2.35 (s, 3H), 2.43 (s, 3H), 3.90 (t, J = 8, 4H),
 4.35-4.45 (m, 4H), 7.00-7.15 (m, 3H).
- 5 al) CI-HRMS: Calcd: 464.1297, Found: 464.1297 (M + H);
 NMR (CDCl₃, 300 MHz): 2.28 (s, 3H), 2.40 (s, 3H),
 3.40 (s, 6H), 3.75 (t, J = 8, 4H), 3.83 (s, 3H),
 4.20-4.50 (m, 4H), 6.93 (dd, J = 8, 1, 1H), 7.20
 10 (s, 1H), 7.24 (d, J = 1, 1H).
- am) CI-HRMS: Calcd: 418.1242, Found: 418.1223 (M + H);
 NMR (CDCl₃, 300 MHz): 1.00 (t, d, J = 8, 1, 6H),
 1.55-1.75 (m, 4H), 2.34 (s, 3H), 2.49 (s, 3H), 2.84
 (s, 3H), 4.15-4.27 (m, 1H), 6.19 (d, J = 8, 1H),
 15 6.93 (dd, J = 8, 1, 1H), 7.21-7.30 (m, 2H).
- an) CI-HRMS: Calcd: 404.1086, Found: 404.1079 (M + H);
 NMR (CDCl₃, 300 MHz): 1.35 (t, J = 8, 6H), 2.28 (s,
 3H), 2.40 (s, 3H), 3.83 (s, 3H), 3.90-4.08 (m, 2H),
 4.08-4.20 (m, 2H), 6.92 (dd, J = 8, 1, 1H), 7.20-
 20 7.25 (m, 2H).
- ao) CI-HRMS: Calcd: 308.1875, Found: 308.1872 (M + H);
 NMR (CDCl₃, 300 MHz): 0.75-0.80 (m, 2H), 0.93-1.00
 (m, 2H), 2.16 (s, 3H), 2.28 (s, 3H), 2.35 (s, 3H),
 2.53 (s, 3H), 3.00-3.10 (m, 1H), 6.50-6.55 (m, 1H),
 25 7.00-7.15 (m, 3H).
- ap) CI-HRMS: Calcd: 397.1988, Found: 397.1984 (M + H);
 NMR (CDCl₃, 300 MHz): 2.43 (s, 3H), 2.50 (s, 3H),
 3.43 (s, 3H), 3.61 (dd, J = 8, 8, 2H), 3.69 (dd, J =
 8, 8, 2H), 3.88 (s, 3H), 4.58-4.70 (m, 1H), 6.75
 30 (d, J = 8, 1H), 7.20 (dd, J = 8, 1, 1H), 7.25 (d, J
 = 1, 1H), 7.40 (s, 1H).
- aq) CI-HRMS: Calcd: 375.2297, Found: 375.2286 (M + H);
 Analysis: Calcd: C: 70.56; H: 7.01; N: 22.44;
 Found: C: 70.49; H: 6.99; N: 22.45;
 35 NMR (CDCl₃, 300 MHz): 0.79-0.85 (m, 2H), 1.00-1.05
 (m, 1H), 2.00 (s, 6H), 2.19 (s, 3H), 2.32 (s, 3H),

- 2.44 (s, 3H), 2.84 (t, $J = 8$, 2H), 3.30-3.40 (m, 1H), 4.50 (t, $J = 8$, 2H), 6.95 (s, 2H).
- ar) CI-HRMS: Calcd: 434.1192, Found: 434.1189 (M + H);
Analysis: Calcd: C: 52.54; H: 5.58; N: 16.12; Br: 18.40; Found: C: 52.75; H: 5.59; N: 16.09; Br: 18.67;
- 5 NMR (CDCl₃, 300 MHz): 2.19 (s, 3H), 2.30 (s, 3H), 2.47 (s, 3H), 3.43 (s, 6H), 3.60 (dd, $J = 8$, 8, 2H), 3.70 (dd, $J = 8, 8$, 2H), 4.58-4.70 (m, 1H), 6.71 (d, $J = 8$, 1H), 7.08 (d, $J = 8$, 1H), 7.37 (dd, $J = 8$, 1, 1H), 7.45 (d, $J = 1$, 1H).
- 10 as) CI-HRMS: Calcd: 448.1348, Found: 448.1332 (M + H);
Analysis: Calcd: C: 53.58; H: 5.85; N: 16.62; Br: 17.82; Found: C: 53.68; H: 5.74; N: 15.52; Br: 13.03;
- 15 NMR (CDCl₃, 300 MHz): 1.95-2.10 (m, 2H), 2.20 (s, 3H), 2.30 (s, 3H), 2.47 (s, 3H), 3.38 (s, 3H), 3.41 (s, 3H), 3.50-3.67 (m, 4H), 4.55-4.70 (m, 1H), 6.89 (d, $J = 8$, 1H), 7.05 (d, $J = 8$, 1H), 7.35 (dd, $J = 8$, 1, 1H), 7.47 (d, $J = 1$, 1H).
- 20 at) CI-HRMS: Calcd: 400.2349, Found: 400.2348 (M + H);
Analysis: Calcd: C: 63.14; H: 7.32; N: 17.53; Found: C: 63.40; H: 7.08; N: 17.14;
- 25 NMR (CDCl₃, 300 MHz): 2.16 (s, 3H), 2.20 (s, 3H), 2.30 (s, 3H), 2.46 (s, 3H), 3.42 (s, 6H), 3.60 (q, $J = 8$, 2H), 3.70 (q, $J = 8$, 2H), 3.85 (s, 3H), 4.59-4.70 (m, 1H), 6.70 (d, $J = 8$, 1H), 6.76 (s, 1H), 6.96 (s, 1H).
- 30 au) CI-HRMS: Calcd: 414.2505, Found: 414.2493 (M + H);
NMR (CDCl₃, 300 MHz): 2.15 (s, 3H), 2.19 (s, 3H), 2.25 (s, 3H), 2.40 (s, 3H), 3.40 (s, 6H), 3.76 (t, $J = 8$, 4H), 3.84 (s, 3H), 4.20-4.45 (m, 4H), 6.77 (s, 1H), 6.93 (s, 1H).
- 35 av) CI-HRMS: Calcd: 368.2450, Found: 368.2447 (M + H);
NMR (CDCl₃, 300 MHz): 1.00 (t, $J = 8$, 6H), 1.55-1.85 (m, 4H), 2.19 (s, 3H), 2.20 (s, 3H), 2.30 (s,

- 3H), 2.47 (s, 3H), 3.88 (s, 3H), 4.10-4.30 (m, 1H), 6.15 (d, J = 8, 1H), 6.78 (s, 1H), 6.98 (s, 1H).
- aw) CI-HRMS: Calcd: 353.2216, Found: 353.2197 (M + H);
 NMR (CDCl₃, 300 MHz): 1.35 (t, J = 8, 6H), 2.17 (s, 3H), 2.19 (s, 3H), 2.28 (s, 3H), 2.40 (s, 3H), 3.85 (s, 3H), 3.90-4.20 (m, 4H), 6.78 (s, 1H), 6.95 (s, 1H).
- ax) CI-HRMS: Calcd: 390.1697, Found: 390.1688 (M + H);
 Analysis: Calcd: C: 58.53; H: 6.20; N: 17.96; Cl: 9.09; Found: C: 58.95; H: 6.28; N: 17.73; Cl: 9.15;
 NMR (CDCl₃, 300 MHz): 2.35 (s, 3H), 2.37 (s, 3H), 2.48 (s, 3H), 3.42 (s, 6H), 3.60 (dd, J = 8, 8, 2H), 3.68 (dd, J = 8, 8, 2H), 4.59-4.72 (m, 1H), 6.72 (d, J = 8, 1H), 7.12 (d, J = 8, 1H), 7.23 (d, J = 8, 1H), 7.32 (s, 1H).
- ay) CI-HRMS: Calcd: 374.1748, Found: 374.1735 (M + H);
 Analysis: Calcd: C: 61.04; H: 6.47; N: 18.73; Cl: 9.48; Found: C: 61.47; H: 6.54; N: 18.23; Cl: 9.61;
 NMR (CDCl₃, 300 MHz): 1.01 (t, J = 8, 3H), 1.62-1.88 (m, 4H), 2.35 (s, 3H), 2.37 (s, 3H), 2.48 (d, J = 1, 3H), 3.40, 3.45 (s, s, 3H), 3.50-3.64 (m, 2H), 4.38-4.47 (m, 1H), 6.53 (d, J = 8, 1H), 7.12 (d, J = 8, 1H), 7.07 (d, J = 8, 1H), 7.12 (s, 1H).
- az) CI-HRMS: Calcd: 404.1853, Found: 404.1839 (M + H);
 NMR (CDCl₃, 300 MHz): 2.29 (s, 3H), 2.38 (s, 3H), 2.40 (s, 3H), 3.40 (s, 6H), 3.76 (t, J = 8, 4H), 4.20-4.45 (m, 4H), 7.11 (d, J = 8, 1H), 7.22 (d, J = 8, 1H), 7.31 (s, 1H).
- ba) CI-HRMS: Calcd: 404.1853, Found: 404.1859 (M + H);
 Analysis: C: 59.47; H: 6.50; N: 17.34; Cl: 8.79; Found: C: 59.73; H: 6.46; N: 17.10; Cl: 8.73;
 NMR (CDCl₃, 300 MHz): 1.95-2.08 (m, 2H), 2.35 (s, 3H), 2.38 (s, 3H), 2.46 (s, 3H), 3.38 (s, 3H), 3.41 (s, 3H), 3.50-3.65 (m, 4H), 4.56-4.70 (m, 1H), 6.85 (d, J = 8, 1H), 7.12 (d, J = 8, 1H), 7.45 (d, J = 8, 1H), 7.32 (s, 1H).

- bb) CI-HRMS: Calcd: 391.2246, Found: 391.2258 (M + H);
Analysis: C: 67.67; H: 6.71; N: 21.52; Found: C:
67.93; H: 6.70; N: 21.48;
NMR (CDCl₃, 300 MHz): 0.76-0.84 (m, 2H), 0.84-0.91
5 (m, 2H), 1.00-1.08 (m, 2H), 2.15 (s, 3H), 2.20 (s,
3H), 2.29 (s, 3H), 2.45 (s, 3H), 2.85 (t, J = 8,
2H), 3.28-3.30 (m, 1H), 3.85 (s, 3H), 6.78 (s, 1H),
6.95 (s, 1H).
- bc) CI-HRMS: Calcd: 386.2192, Found: 386.2181 (M + H);
10 Analysis: C: 62.32; H: 7.06; N: 18.17; Found: C:
62.48; H: 6.83; N: 18.15;
NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 8), 6.9 (d,
1H, J = 1), 6.8 (dd, 1H, J = 8,1), 6.7 (br.d, 1H,
J = 8), 4.7-4.6 (m, 1H), 3.85 (s, 3H), 3.70-3.55
15 (m, 4H), 3.45 (s, 6H), 2.5 (s, 3H), 2.3 (s, 3H),
2.15 (s, 3H).
- bd) CI-HRMS: Calcd: 400.2349, Found: 400.2336 (M + H);
NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 7), 6.85 (d,
1H, J = 1), 6.75 (dd, 1H, J = 7,1), 4.45-4.25
20 (br.s, 4H), 3.75 (t, 4H, J = 7), 3.4 (s, 6H), 2.4
(s, 3H), 2.25 (s, 3H), 2.15 (s, 3H).
- be) CI-HRMS: Calcd: 370.2243, Found: 370.2247 (M + H);
Analysis: C: 65.02; H: 7.38; N: 18.96; Found: C:
65.28; H: 7.27; N: 18.71;
25 NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 8), 6.85 (d,
1H, J = 1), 6.8 (dd, 1H, J = 8,1), 6.5 (br. d, 1H,
J = 1), 4.5-4.3 (m, 1H), 3.85 (s, 3H), 3.65-3.5 (m,
2H), 3.4 (s, 2H), 2.5 (s, 3H), 2.3 (s, 3H), 2.2 (s,
3H), 1.9-1.7 (m, 2H), 1.05 (t, 3H, J = 7).
- 30 bf) CI-HRMS: Calcd: 379.2246, Found: 379.2248 (M + H);
NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 8), 6.85 (d,
1H, J = 1), 6.8 (dd, 1H, J = 8,1), 4.3-4.0 (m, 4H),
3.85 (s, 3H), 3.0 (t, 2H, J = 7), 2.45 (s, 3H), 2.3
(s, 3H), 2.2 (s, 3H), 1.9-1.8 (m, 2H), 1.0 (t, 3H,
35 J = 7).
- bg) CI-HRMS: Calcd: 340.2137, Found: 340.2122 (M + H);

- NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 8), 6.85 (d, 1H, J = 1), 6.75 (dd, 1H, J = 8, 1), 4.2-4.0 (br.m, 4H), 3.85 (s, 3H), 2.4 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 1.35 (t, 6H, J = 7).
- 5 bh) CI-HRMS: Calcd: 313.1665, Found: 313.6664 (M + H).
 bi) CI-HRMS: Calcd: 400.2349, Found: 400.2346 (M + H);
 NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 7), 6.9-6.75 (m, 3H), 4.7-4.55 (m, 1H), 3.8 (s, 3H), 3.7-3.5 (m, 4H), 3.45 (s, 3H), 3.35 (s, 3H), 2.5 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 2.1-1.95 (m, 2H).
- 10 bj) CI-HRMS: Calcd: 377.2090, Found: 377.2092 (M + H);
 Analysis: C: 67.00; H: 6.44; N: 22.32; Found: C: 67.35; H: 6.44; N: 22.23;
 NMR (CDCl₃, 300 MHz): 7.1 (d, 1H, J = 8), 6.9 (d, 1H, J = 1), 6.8 (dd, 1H, J = 8, 1), 4.55-4.4 (m, 2H), 3.85 (s, 3H), 3.4-3.3 (m, 1H), 2.85 (t, 2H, J = 7), 2.5 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 1.1-1.0 (m, 2H), 0.85-0.75 (m, 2H).
- 15 bk) CI-HRMS: Calcd: 413.2427, Found: 413.2416 (M + H);
 20 NMR (CDCl₃, 300Hz): 7.1 (d, 1H, J = 8), 6.85 (d, 1H, J = 1), 6.75 (dd, 1H, J = 8, 1), 4.6 (m, 1H), 3.85 (s, 3H), 3.75-3.6 (m, 4H), 3.6 (q, 4H, J = 7), 2.5 (s, 3H), 2.3 s, 3H), 2.2 (s, 3H), 1.25 (t, 6H, J = 7).
- 25 bl) CI-HRMS: Calcd: 420.1802, Found: 420.1825 (M + H);
 bm) CI-HRMS: Calcd: 390.1697, Found: 390.1707 (M + H);
 bn) CI-HRMS: Calcd: 397.1465, Found: 397.1462 (M + H);
 bo) CI-HRMS: Calcd: 360.1513, Found: 360.1514 (M + H);
 bp) CI-HRMS: Calcd: 374.1748, Found: 374.1737 (M + H);
 30 bq) CI-HRMS: Calcd: 479.1155, Found: 479.1154 (M + H);
 br) CI-HRMS: Calcd: 463.1219, Found: 463.1211 (M + H);
 Analysis Calcd: C: 51.96, H: 5.23, N: 15.15, Br: 17.28; Found: C: 52.29, H: 5.62, N: 14.79, Br: 17.47
- 35 bs) CI-HRMS: Calcd: 433.1113, Found: 433.1114 (M, ⁷⁹Br);
 bt) NH₃-CI MS: Calcd: 406, Found: 406 (M + H)+;

NMR (CDCl₃, 300 MHz) : δ 7.28 (d, J=10Hz, 1H), 7.03 (d, J=8Hz, 1H), 6.96 (s, 1H), 6.7 (d, J=9, 1H), 4.63 (m, 1H), 3.79 (s, 3H), 3.6 (m, 4H), 3.42 (s, 6H), 2.47 (s, 3H), 2.32 (s, 3H).

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EXAMPLE 431

Preparation of 2,4,7-dimethyl-8-(4-methoxy-2-methylphenyl)[1,5-a]-pyrazolo-1,3,5-triazine (Formula 1, where R³ is CH₃, R₁ is CH₃, Z is C-CH₃, Ar is 2,4-dimethylphenyl)

5-Acetamidino-4-(4-methoxy-2-methylphenyl)-3-methylpyrazole, acetic acid salt (602 mg, 2 mmol) was mixed with a saturated NaHCO₃ solution (10 mL). The aqueous mixture was extracted with EtOAc three times. The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The residue was taken up in toluene (10 mL) and trimethyl orthoacetate (0.36 g, 3 mmol) was added to the suspension. The reaction mixture was heated to reflux temperature under a nitrogen atmosphere and stirred for 16 hours. After being cooled to ambient temperature, the reaction mixture was concentrated in vacuo to give an oily solid. Column chromatography (CHCl₃:MeOH::9:1) afforded, after removal of solvent in vacuo, a yellow viscous oil (R_f = 0.6, 210 mg, 37% yield): NMR (CDCl₃, 300 MHz): 7.15 (d, 1H, J = 8), 6.9 (d, 1H, J = 1), 6.85 (dd, 1H, J = 8,1), 3.85 (s, 3H), 2.95 (s, 3H), 2.65 (s, 3H), 2.4 (s, 3H), 2.15 (s, 3H); CI-HRMS: Calcd: 283.1559, Found: 283.1554 (M + H).

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EXAMPLE 432

7-hydroxy-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine
(Formula 1 where A is CH, R1 is Me, R3 is OH,
Z is C-Me, Ar is 2-chloro-4-methylphenyl)

5-Amino-4-(2-chloro-4-methylphenyl)-3-methylpyrazole (1.86 g, 8.4 mmol) was dissolved in glacial acetic acid (30 mL) with stirring. Ethyl acetoacetate (1.18 mL, 9.2 mmol) was then added dropwise to the resulting solution. The reaction mixture was then heated to reflux temperature and stirred for 16 hours, then cooled to room temperature. Ether (100 mL) was added and the resulting precipitate was collected by filtration. Drying in vacuo afforded a white solid (1.0 g, 42% yield): NMR (CDCl₃, 300Hz): 8.70 (br.s 1H), 7.29 (s, 1H), 7.21-7.09 (m, 2H), 5.62 (s, 1H), 2.35 (s, 6H), 2.29 (s, 3H); CI-MS: 288 (M+H).

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EXAMPLE 433

7-chloro-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine
(Formula 1 where A is CH, R1 is Me, R3 is Cl,
Z is C-Me, Ar is 2-chloro-4-methylphenyl)

25

A mixture of 7-hydroxy-5-methyl-3-(2-chloro-4-methylphenyl)-pyrazolo[1,5-a]pyrimidine (1.0 g, 3.5 mmol), phosphorus oxychloride (2.7 g, 1.64 mL, 17.4 mmol), N,N-diethylaniline (0.63 g, 0.7 mL, 4.2 mmol) and toluene (20 mL) was stirred at reflux temperature for 3 hours, then it was cooled to ambient temperature. The volatiles were removed in vacuo. Flash chromatography (EtOAc:hexane::1:2) on the residue gave 7-chloro-5-methyl-3-(2-chloro-4-methylphenyl)-pyrazolo[1,5-a]pyrimidine (900 mg, 84% yield) as a yellow oil: NMR

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(CDCl₃, 300Hz): 7.35 (s, 1H), 7.28-7.26 (m, 1H), 71.6 (d, 1H, J = 7), 6.80 (s, 1H), 2.55 (s, 3H), 2.45 (s, 3H), 2.40 (s, 3H); CI- MS: 306 (M+H).

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EXAMPLE 434

7-(pentyl-3-amino)-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine

(Formula 1 where A is CH, R₁ is Me, R₃ is pentyl-3-amino, Z is C-Me, Ar is 2-chloro-4-methylphenyl)

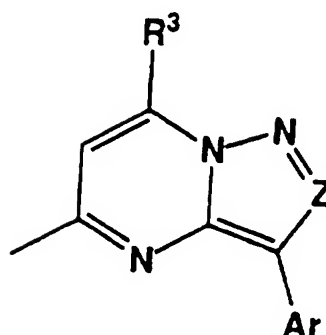
A solution of 3-pentylamine (394mg, 6.5 mmol) and 7-chloro-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine (200 mg, 0.65 mmol) in dimethylsulfoxide (DMSO, 10 mL) was stirred at 150°C for 2 hours; then it was cooled to ambient temperature. The reaction mixture was then poured onto water (100 mL) and mixed. Three extractions with dichloromethane, washing the combined organic layers with brine, drying over MgSO₄, filtration and removal of solvent in vacuo produced a yellow solid. Flash chromatography (EtOAc:hexanes::1:4) afforded a white solid (140 mg, 60% yield): mp 139-141°C; NMR (CDCl₃, 300Hz): 7.32 (s, 1H), 7.27 (d, 1H, J = 8), 7.12 (d, 1H, J = 7), 6.02 (d, 1H, J = 9), 5.78 (s, 1H), 3.50-3.39 (m, 1H), 2.45 (s, 3H), 2.36 (s, 6H), 1.82-1.60 (m, 4H), 1.01 (t, 6H, J = 8); Analysis Calcd for C₂₀H₂₅ClN₄: C, 67.31, H, 7.06, N, 15.70, Cl: 9.93; Found: C, 67.32, H, 6.95, N, 15.50, Cl, 9.93.

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The examples delineated in TABLE 2 may be prepared by the methods outlined in Examples 1A, 1B, 432, 433, 434. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example, EtOAc is ethyl acetate.

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TABLE 2



| | Ex. | Z | R ³ | Ar | mp (°C) |
|----|------|------|---|-------------------------|----------|
| 5 | 435b | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2,4-Cl ₂ -Ph | 71-73 |
| | 436c | C-Me | N(Bu)Et | 2,4-Cl ₂ -Ph | 86-87 |
| | 437d | C-Me | NHCH(Et)CH ₂ OMe | 2,4-Cl ₂ -Ph | 110-111 |
| | 438e | C-Me | N(Pr)CH ₂ CH ₂ CN | 2,4-Cl ₂ -Ph | 83-85 |
| 10 | 439f | C-Me | NH-3-pentyl | 2,4-Cl ₂ -Ph | 175-176 |
| | 440g | C-Me | NHCH(CH ₂ OMe) ₂ | 2,4-Cl ₂ -Ph | 107 |
| | 441h | C-Me | NHCH(Et) ₂ | 2,4-Me ₂ -Ph | oil |
| | 442i | C-Me | NHCH(CH ₂ OMe) ₂ | 2,4-Me ₂ -Ph | 103-105 |
| | 443j | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2,4-Me ₂ -Ph | 87-89 |
| 15 | 444k | C-Me | N(c-Pr)CH ₂ CH ₂ CN | 2,4-Me ₂ -Ph | 133(dec) |
| | 445l | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Cl, 4-MePh | 77-78 |
| | 446m | C-Me | NHCH(CH ₂ OMe) ₂ | 2-Cl, 4-MePh | 131-133 |
| | 447n | C-Me | NHCH(Et) ₂ | 2-Cl, 4-MePh | 139-141 |
| | 448o | C-Me | NEt ₂ | 2,4-Me ₂ -Ph | 92-94 |
| 20 | 449p | C-Me | N(Pr)CH ₂ CH ₂ CN | 2,4-Me ₂ -Ph | 143-144 |
| | 450q | C-Me | N(Bu)CH ₂ CH ₂ CN | 2,4-Me ₂ -Ph | 115-117 |
| | 451r | C-Me | NHCH(Et)CH ₂ OMe | 2,4-Me ₂ -Ph | oil |
| | 452s | C-Me | NHCH(Et) ₂ | 2-Me, 4-MeOPh | 104-106 |
| | 453t | C-Me | NHCH(CH ₂ OMe) ₂ | 2-Me, 4-MeOPh | 115-116 |
| 25 | 454u | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Me, 4-MeOPh | oil |
| | 455v | C-Me | (S)-NHCH(CH ₂ CH ₂ OMe)-(CH ₂ OMe) | 2-Me, 4-MeOPh | oil |
| | 456w | C-Me | (S)-NHCH(CH ₂ CH ₂ OMe)-(CH ₂ OMe) | 2,4-Me ₂ -Ph | oil |

| | | | | | |
|----|-------------------|------|--|---------------------------------|---------|
| | 457 ^x | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Me, 4-ClPh | oil |
| | 458 ^y | C-Me | NHEt | 2, 4-Me ₂ -Ph | oil |
| | 459 ^z | C-Me | NHCH(Et) ₂ | 2-Me, 4-ClPh | 94-96 |
| | 460 ^{aa} | C-Me | NHCH(CH ₂ OMe) ₂ | 2-Me, 4-ClPh | 113-114 |
| 5 | 461 ^{ab} | C-Me | N(Ac)Et | 2, 4-Me ₂ -Ph | oil |
| | 462 ^{ac} | C-Me | (S)-NHCH(CH ₂ CH ₂ OMe) - (CH ₂ OMe) | 2-Me, 4-ClPh | oil |
| | 463 ^{ad} | C-Me | N(Pr)CH ₂ CH ₂ CN | 2-Me, 4-MeOPh | 118-119 |
| | 464 ^{ae} | C-Me | NEt ₂ | 2-Me, 4-MeOPh | 97-99 |
| 10 | 465 ^{af} | C-Me | (S)-NHCH(CH ₂ CH ₂ OMe) - (CH ₂ OMe) | 2-Cl, 4-MePh | 101-103 |
| | 466 ^{ag} | C-Me | NEt ₂ | 2-Cl, 4-MePh | 129-130 |
| | 467 ^{ah} | C-Me | N(c-Pr)CH ₂ CH ₂ CN | 2-Me, 4-MeOPh | 177-178 |
| | 468 ^{ai} | C-Me | N(c-Pr)CH ₂ CH ₂ CN | 2-Cl, 4-MePh | 162-163 |
| 15 | 469 ^{aj} | C-Me | NHCH(Et)CH ₂ OMe | 2-Me, 4-MeOPh | oil |
| | 470 ^{ak} | C-Me | NHCH(Et)CH ₂ OMe | 2-Cl, 4-MePh | 111-113 |
| | 471 | C-Me | NHCH(CH ₂ OMe) ₂ | 2-Cl-4-MeOPh | |
| | 472 | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Cl-4-MeOPh | |
| | 473 | C-Me | NHCH(Et)CH ₂ OMe | 2-Cl-4-MeOPh | |
| 20 | 474 | C-Me | N(c-Pr)CH ₂ CH ₂ CN | 2-Cl-4-MeOPh | |
| | 475 | C-Me | NEt ₂ | 2-Cl-4-MeOPh | |
| | 476 | C-Me | NH-3-pentyl | 2-Cl-4-MeOPh | |
| | 477 | C-Me | NHCH(Et)CH ₂ CH ₂ OMe | 2-Cl-4-MeOPh | |
| | 478 | C-Me | NHCH(Me)CH ₂ CH ₂ OMe | 2-Cl-4-MeOPh | |
| 25 | 479 | C-Me | NHCH(Et)CH ₂ CH ₂ OMe | 2-Br-4-MeOPh | |
| | 480 | C-Me | NHCH(Me)CH ₂ CH ₂ OMe | 2-Br-4-MeOPh | |
| | 481 | C-Me | NHCH(Et)CH ₂ CH ₂ OMe | 2-Me-4-MeOPh | |
| | 482 | C-Me | NHCH(Me)CH ₂ CH ₂ OMe | 2-Me-4-MeOPh | |
| | 483 | C-Me | NHCH(CH ₂ OMe) ₂ | 2-Cl-4, 5-(MeO) ₂ Ph | |
| 30 | 484 | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Cl-4, 5-(MeO) ₂ Ph | |
| | 485 | C-Me | NHCH(Et)CH ₂ OMe | 2-Cl-4, 5-(MeO) ₂ Ph | |
| | 486 | C-Me | N(c-Pr)CH ₂ CH ₂ CN | 2-Cl-4, 5-(MeO) ₂ Ph | |
| | 487 | C-Me | NEt ₂ | 2-Cl-4, 5-(MeO) ₂ Ph | 99-101 |
| | 488 | C-Me | NH-3-pentyl | 2-Cl-4, 5-(MeO) ₂ Ph | 169-170 |
| 35 | 489 | C-Me | NHCH(Et)CH ₂ CH ₂ OMe | 2-Cl-4, 5-(MeO) ₂ Ph | |

| | | | | | |
|----|-----|------|--|----------------------------------|-------|
| | 490 | C-Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-Cl-4, 5- (MeO) ₂ Ph | |
| | 491 | C-Me | NHCH (CH ₂ OMe) ₂ | 2-Br-4, 5- (MeO) ₂ Ph | 90-93 |
| | 492 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2-Br-4, 5- (MeO) ₂ Ph | 110 |
| | 493 | C-Me | NHCH (Et) CH ₂ OMe | 2-Br-4, 5- (MeO) ₂ Ph | |
| 5 | 494 | C-Me | N (c-Pr) CH ₂ CH ₂ CN | 2-Br-4, 5- (MeO) ₂ Ph | |
| | 495 | C-Me | NEt ₂ | 2-Br-4, 5- (MeO) ₂ Ph | |
| | 496 | C-Me | NH-3-pentyl | 2-Br-4, 5- (MeO) ₂ Ph | |
| | 497 | C-Me | NHCH (Et) CH ₂ CH ₂ OMe | 2-Br-4, 5- (MeO) ₂ Ph | |
| | 498 | C-Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-Br-4, 5- (MeO) ₂ Ph | |
| 10 | 499 | C-Me | NHCH (CH ₂ OMe) ₂ | 2-Cl-4, 6- (MeO) ₂ Ph | |
| | 500 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2-Cl-4, 6- (MeO) ₂ Ph | |
| | 501 | C-Me | NHCH (Et) CH ₂ OMe | 2-Cl-4, 6- (MeO) ₂ Ph | |
| | 502 | C-Me | N (c-Pr) CH ₂ CH ₂ CN | 2-Cl-4, 6- (MeO) ₂ Ph | |
| | 503 | C-Me | NEt ₂ | 2-Cl-4, 6- (MeO) ₂ Ph | |
| 15 | 504 | C-Me | NH-3-pentyl | 2-Cl-4, 6- (MeO) ₂ Ph | |
| | 505 | C-Me | NHCH (Et) CH ₂ CH ₂ OMe | 2-Cl-4, 6- (MeO) ₂ Ph | |
| | 506 | C-Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-Cl-4, 6- (MeO) ₂ Ph | |
| | 507 | C-Me | NHCH (CH ₂ OMe) ₂ | 2-Me-4, 6- (MeO) ₂ Ph | |
| | 508 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2-Me-4, 6- (MeO) ₂ Ph | |
| 20 | 509 | C-Me | NHCH (Et) CH ₂ OMe | 2-Me-4, 6- (MeO) ₂ Ph | |
| | 510 | C-Me | N (c-Pr) CH ₂ CH ₂ CN | 2-Me-4, 6- (MeO) ₂ Ph | |
| | 511 | C-Me | NEt ₂ | 2-Me-4, 6- (MeO) ₂ Ph | |
| | 512 | C-Me | NH-3-pentyl | 2-Me-4, 6- (MeO) ₂ Ph | |
| | 513 | C-Me | NHCH (Et) CH ₂ CH ₂ OMe | 2-Me-4, 6- (MeO) ₂ Ph | |
| 25 | 514 | C-Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-Me-4, 6- (MeO) ₂ Ph | |
| | 515 | C-Me | N (c-Pr) CH ₂ CH ₂ CN | 2-Br-4, 6- (MeO) ₂ Ph | |
| | 516 | C-Me | NEt ₂ | 2-Br-4, 6- (MeO) ₂ Ph | |
| | 517 | C-Me | NH-3-pentyl | 2-Br-4, 6- (MeO) ₂ Ph | |
| | 518 | C-Me | NHCH (Et) CH ₂ CH ₂ OMe | 2-Br-4, 6- (MeO) ₂ Ph | |
| 30 | 519 | C-Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-Br-4, 6- (MeO) ₂ Ph | |
| | 520 | C-Me | NHCH (Et) CH ₂ CH ₂ OMe | 2-Me-4-MeOPh | |
| | 521 | C-Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-Me-4-MeOPh | |
| | 522 | C-Me | NHCH (CH ₂ OMe) ₂ | 2-MeO-4-MePh | |
| | 523 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2-MeO-4-MePh | |
| 35 | 524 | C-Me | NHCH (Et) CH ₂ OMe | 2-MeO-4-MePh | |
| | 525 | C-Me | N (c-Pr) CH ₂ CH ₂ CN | 2-MeO-4-MePh | |

| | | | | |
|----|-----|------|---|--------------|
| | 526 | C-Me | NEt ₂ | 2-MeO-4-MePh |
| | 527 | C-Me | NH-3-pentyl | 2-MeO-4-MePh |
| | 528 | C-Me | NHCH(Et)CH ₂ CH ₂ OMe | 2-MeO-4-MePh |
| | 529 | C-Me | NHCH(Me)CH ₂ CH ₂ OMe | 2-MeO-4-MePh |
| 5 | 530 | C-Me | NHCH(CH ₂ OMe) ₂ | 2-MeO-4-MePh |
| | 531 | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-MeO-4-MePh |
| | 532 | C-Me | NHCH(Et)CH ₂ OMe | 2-MeO-4-MePh |
| | 533 | C-Me | N(c-Pr)CH ₂ CH ₂ CN | 2-MeO-4-MePh |
| | 534 | C-Me | NEt ₂ | 2-MeO-4-MePh |
| 10 | 535 | C-Me | NH-3-pentyl | 2-MeO-4-MePh |
| | 536 | C-Me | NHCH(Et)CH ₂ CH ₂ OMe | 2-MeO-4-MePh |
| | 537 | C-Me | NHCH(Me)CH ₂ CH ₂ OMe | 2-MeO-4-MePh |
| | 538 | C-Me | NHCH(CH ₂ OMe) ₂ | 2-MeO-4-ClPh |
| | 539 | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-MeO-4-ClPh |
| 15 | 540 | C-Me | NHCH(Et)CH ₂ OMe | 2-MeO-4-ClPh |
| | 541 | C-Me | N(c-Pr)CH ₂ CH ₂ CN | 2-MeO-4-ClPh |
| | 542 | C-Me | NEt ₂ | 2-MeO-4-ClPh |
| | 543 | C-Me | NH-3-pentyl | 2-MeO-4-ClPh |
| | 544 | C-Me | NHCH(Et)CH ₂ CH ₂ OMe | 2-MeO-4-ClPh |
| 20 | 545 | C-Me | NHCH(Me)CH ₂ CH ₂ OMe | 2-MeO-4-ClPh |

NOTES FOR TABLE 2:

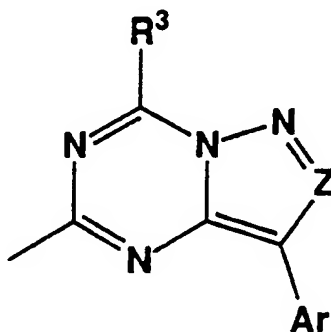
- b) CI-HRMS: Calcd: 423.1355; Found: 423.1337 (M + H).
- 25 c) Analysis: Calcd: C, 61.38, H, 6.18, N, 14.32;
Found: C, 61.54, H, 6.12, N, 14.37.
- d) Analysis: Calcd: C: 58.02, H, 5.65, N, 14.24;
Found: C, 58.11, H, 5.52, N, 14.26.
- e) Analysis: Calcd: C, 59.71, H, 5.26, N, 14.85;
30 Found: C, 59.94, H, 5.09, N, 17.23.
- f) Analysis: Calcd: C, 60.48, H, 5.89, N, 14.85,
Found: C, 60.62, H, 5.88, N, 14.82.
- h) CI-HRMS: Calcd: 337.2388; Found: 337.2392 (M + H).
- i) Analysis: Calcd: C, 68.45, H, 7.669, N, 15.21,
35 Found: C, 68.35, H, 7.49 N, 14.91.

- j) Analysis: Calcd: C, 69.08, H, 7.915, N, 14.65,
Found: C, 68.85, H, 7.83, N, 14.54.
- k) Analysis: Calcd: C, 73.51, H, 7.01, N, 19.48,
Found: C, 71.57, H, 7.15, N, 19.12.
- 5 l) CI-HRMS: Calcd: 403.1899; Found: 403.1901 (M + H).
m) Analysis: Calcd: C, 61.77, H, 6.49, N, 14.41, Cl,
9.13; Found: C, 61.90, H, 6.66, N, 13.62, Cl, 9.25.
- n) Analysis: Calcd: C, 67.31, H, 7.06, N, 15.70, Cl,
9.93; Found: C, 67.32, H, 6.95, N, 15.50, Cl, 9.93.
- 10 o) Analysis: Calcd: C, 74.50, H, 8.14, N, 17.38,
Found: C, 74.43, H, 7.59, N, 17.16.
- p) Analysis: Calcd: C, 73.10, H, 7.54, N, 19.37,
Found: C, 73.18, H, 7.59, N, 18.81.
- 15 q) Analysis: Calcd: C, 73.57, H, 7.78, N, 18.65,
Found: C, 73.55, H, 7.79, N, 18.64.
- r) CI-HRMS: Calcd: 353.2333; Found: 353.2341 (M + H).
- s) Analysis: Calcd: C, 71.56, H, 8.02, N, 15.90,
Found: C, 71.45, H, 7.99, N, 15.88.
- 20 t) Analysis: Calcd: C, 65.60, H, 7.34, N, 14.57,
Found: C, 65.42, H, 7.24, N, 14.37.
- u) CI-HRMS: Calcd: 399.2398; Found: 399.2396 (M + H).
- v) CI-HRMS: Calcd: 399.2398; Found: 399.2396 (M + H).
- w) CI-HRMS: Calcd: 383.2450; Found: 383.2447 (M + H).
- x) CI-HRMS: Calcd: 403.1887; Found: 403.1901 (M + H).
- 25 y) CI-HRMS: Calcd: 295.1919; Found: 295.1923 (M + H).
- z) Analysis: Calcd: C, 67.31, H, 7.06, N, 15.70,
Found: C, 67.12, H, 6.86, N, 15.53.
- aa) Analysis: Calcd: C, 61.77, H, 6.49, N, 14.41, Cl,
9.13; Found: C, 62.06, H, 6.37, N, 14.25, Cl, 9.12.
- 30 ab) CI-HRMS: Calcd: 337.2017; Found: 337.2028 (M + H).
- ac) CI-HRMS: Calcd: 403.1893; Found: 403.1901 (M + H).
- ad) Analysis: Calcd: C, 70.00, H, 7.22, N, 18.55,
Found: C, 70.05, H, 7.22, N, 18.36.
- ae) Analysis: Calcd: C, 70.98, H, 7.74, N, 16.55,
35 Found: C, 71.15, H, 7.46, N, 16.56.

- ag) Analysis: Calcd: C, 66.59, H, 6.76, N, 16.34,
Found: C, 66.69, H, 6.82, N, 16.20.
- ah) Analysis: Calcd: C, 70.38, H, 6.71, N, 18.65,
Found: C, 70.35, H, 6.82, N, 18.83.
- 5 ai) Analysis: Calcd: C, 66.39, H, 5.85, N, 18.44, Cl,
9.33;
Found: C, 66.29, H, 5.51, N, 18.36, Cl, 9.31.
- aj) CI-HRMS: Calcd: 369.2278; Found: 369.2291 (M + H).
- ak) Analysis: Calcd: C, 64.42, H, 6.77, N, 15.02,
10 Found: C, 64.59, H, 6.51, N, 14.81.

The examples delineated in TABLE 3 may be prepared by
the methods outlined in Examples 1, 2, 3 or 6. Commonly
15 used abbreviations are: Ph is phenyl, Pr is propyl, Me
is methyl, Et is ethyl, Bu is butyl, Ex is Example.

TABLE 3



| Ex. | Z | R ₃ | Ar | mp (°C) |
|---------------------|------|---|-----------------------------|---------|
| 546 ^a | C-Me | NHCH(Et) ₂ | 2-Me-4-Me ₂ N-Ph | 164-166 |
| 25 547 ^b | C-Me | S-NHCH(CH ₂ CH ₂ OMe) -CH ₂ OMe | 2,4-Me ₂ -Ph | oil |
| 548 ^c | C-Me | S-NHCH(CH ₂ CH ₂ OMe) -CH ₂ OMe | 2-Me-4-Cl-Ph | oil |
| 549 ^d | C-Me | N(c-Pr)CH ₂ CH ₂ CN | 2-Me-4-Cl-Ph | 115-116 |

| | | | | | |
|----|------------------|------|--|---------------------------------|-----------|
| | 550 ^e | C-Me | NHCH (Et) CH ₂ CN | 2-Me-4-Cl-Ph | 131-132 |
| | 551 ^f | C-Me | N (Et) ₂ | 2,3-Me ₂ -4-OMe-Ph | oil |
| | 552 ^g | C-Me | N (CH ₂ CH ₂ OMe) CH ₂ CH ₂ OH | 2,4-Cl ₂ -Ph | oil |
| | 553 ^h | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2,3-Me ₂ -4-OMe-Ph | oil |
| 5 | 554 ⁱ | C-Me | NHCH (Et) ₂ | 2,3-Me ₂ -4-OMePh | 123-124 |
| | 555 ^j | C-Me | N (CH ₂ -c-Pr) Pr | 2-Me-4-Cl-Ph | oil |
| | 556 ^k | C-Me | N (c-Pr) CH ₂ CH ₂ CN | 2,3-Me ₂ -4-OMePh | 158-160 |
| | 557 | C-Me | N (c-Pr) Et | 2-Cl-4-OMePh | |
| | 558 | C-Me | N (c-Pr) Me | 2-Cl-4-OMePh | |
| 10 | 559 | C-Me | N (c-Pr) Pr | 2-Cl-4-OMePh | |
| | 560 | C-Me | N (c-Pr) Bu | 2-Cl-4-OMePh | |
| | 561 ^l | C-Me | N (Et) ₂ | 2-Cl-4-CN-Ph | 115-117 |
| | 562 | C-Me | N (c-Pr) ₂ | 2-Cl-4-OMe | 127-129 |
| | 563 ^m | C-Me | NHCH (CH ₂ OH) ₂ | 2,4-Cl ₂ -Ph | 128-129 |
| 15 | 564 | C-Me | N (c-Pr) Et | 2-Br-4,5- (MeO) ₂ Ph | |
| | 565 | C-Me | N (c-Pr) Me | 2-Br-4,5- (MeO) ₂ Ph | |
| | 566 | C-Me | NH-c-Pr | 2-Me-4-MeOPh | 126-128 |
| | 567 | C-Me | NHCH (Et) CH ₂ OH | 2-Me-4-MeOPh | 60-62 |
| | 568 | C-Me | NMe ₂ | 2-Br-4,5- (MeO) ₂ Ph | |
| 20 | 569 | C-Me | NHCH (Et) ₂ | 2-Me-4-MeOPh | 103-105 |
| | 570 | C-Me | N (c-Pr) Et | 2-Me-4-MeOPh | 173-174 |
| | 571 | C-Me | NH-2-pentyl | 2,4-Cl ₂ -Ph | 118-120 |
| | 572 | C-Me | NHCH (Et) CH ₂ CN | 2,4-Cl ₂ -Ph | 141-142 |
| | 573 | C-Me | NHCH (Pr) CH ₂ OMe | 2,4-Cl ₂ -Ph | 87-88 |
| 25 | 574 | C-Me | NHCH (CH ₂ -iPr) CH ₂ OMe | 2,4-Cl ₂ -Ph | amorphous |
| | 575 | C-Me | NH-2-butyl | 2,4-Me ₂ -Ph | oil |
| | 576 | C-Me | NH-2-pentyl | 2,4-Me ₂ -Ph | oil |
| | 577 | C-Me | NH-2-hexyl | 2,4-Me ₂ -Ph | oil |
| | 578 | C-Me | NHCH (i-Pr) Me | 2,4-Me ₂ -Ph | oil |
| 30 | 579 | C-Me | NHCH (Me) CH ₂ -iPr | 2,4-Me ₂ -Ph | oil |
| | 580 | C-Me | NHCH (Me) -c-C ₆ H ₁₁ | 2,4-Me ₂ -Ph | oil |
| | 581 | C-Me | NH-2-indanyl | 2,4-Me ₂ -Ph | oil |
| | 582 | C-Me | NH-1-indanyl | 2,4-Me ₂ -Ph | oil |
| | 583 | C-Me | NHCH (Me) Ph | 2,4-Me ₂ -Ph | oil |
| 35 | 584 | C-Me | NHCH (Me) CH ₂ - (4-ClPh) | 2,4-Me ₂ -Ph | oil |

| | | | | | |
|----|------------------|--------|--|---------------------------------|---------|
| | 585 | C-Me | NHCH (Me) CH ₂ COCH ₃ | 2,4-Me ₂ -Ph | oil |
| | 586 | C-Me | NHCH (Ph) CH ₂ Ph | 2,4-Me ₂ -Ph | oil |
| | 587 | C-Me | NHCH (Me) (CH ₂) ₃ NEt ₂ | 2,4-Me ₂ -Ph | oil |
| | 588 | C-Me | NH- (2-Ph-c-C ₃ H ₄) | 2,4-Me ₂ -Ph | oil |
| 5 | 589 | C-Me | NHCH (Et) CH ₂ CN | 2,4-Me ₂ -Ph | 119-120 |
| | 590 | C-Me | NH-3-hexyl | 2,4-Me ₂ -Ph | oil |
| | 591 ⁿ | C-Me | NEt ₂ | 2-MeO-4-ClPh | oil |
| | 592 ^o | C-Me | NHCH (Et) ₂ | 2-MeO-4-ClPh | oil |
| | 593 ^p | C-Me | NHCH (Et) CH ₂ OMe | 2-MeO-4-ClPh | oil |
| 10 | 594 | C-Me | NMe ₂ | 2-MeO-4-ClPh | oil |
| | 595 ^q | C-Me | NHCH (Et) ₂ | 2-OMe-4-MePh | oil |
| | 596 ^r | C-Me | NEt ₂ | 2-OMe-4-MePh | oil |
| | 597 ^s | C-c-Pr | NHCH (CH ₂ OMe) ₂ | 2,4-Cl ₂ -Ph | oil |
| | 598 | C-Me | N (c-Pr) Et | 2,4-Me ₂ -Ph | |
| 15 | 599 | C-Me | N (c-Pr) Et | 2,4-Cl ₂ -Ph | |
| | 600 | C-Me | N (c-Pr) Et | 2,4,6-Me ₃ -Ph | |
| | 601 | C-Me | N (c-Pr) Et | 2-Me-4-Cl-Ph | |
| | 602 | C-Me | N (c-Rr) Et | 2-Cl-4-Me-Ph | |
| | 603 | C-Me | NHCH (c-Pr) ₂ | 2,4-Cl ₂ -Ph | |
| 20 | 604 | C-Me | NHCH (c-Pr) ₂ | 2,4-Me ₂ -Ph | |
| | 605 | C-Me | NHCH (c-Pr) ₂ | 2-Me-4-Cl-Ph | |
| | 606 | C-Me | NHCH (c-Pr) ₂ | 2-Cl-4-Me-Ph | |
| | 607 | C-Me | NHCH (c-Pr) ₂ | 2-Me-4-OMe-Ph | |
| | 608 | C-Me | NHCH (c-Pr) ₂ | 2-Cl-4-OMe-Ph | |
| 25 | 609 | C-Me | NHCH (CH ₂ OMe) ₂ | 2-Cl-5-F-OMePh | |
| | 610 | C-Me | NEt ₂ | 2-Cl-5-F-OMePh | |
| | 611 | C-Me | N (c-Pr) CH ₂ CH ₂ CN | 2-Cl-5-F-OMePh | |
| | 612 | C-Me | NHCH (Et) ₂ | 2-Cl-5-F-OMePh | |
| | 613 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2-Cl-5-F-OMePh | |
| 30 | 614 | C-Me | NEt ₂ | 2,6-Me ₂ -pyrid-3-yl | |
| | 615 | C-Me | N (c-Pr) CH ₂ CH ₂ CN | 2,6-Me ₂ -pyrid-3-yl | |
| | 616 | C-Me | NHCH (Et) ₂ | 2,6-Me ₂ -pyrid-3-yl | |
| | 617 | C-Me | N (CH ₂ CH ₂ OMe) ₂ | 2,6-Me ₂ -pyrid-3-yl | |
| | 618 | C-OH | NHCH (CH ₂ OMe) ₂ | 2,4-Me ₂ -Ph | |
| 35 | 619 | C-OH | NEt ₂ | 2,4-Me ₂ -Ph | |
| | 620 | C-OH | N (c-Pr) CH ₂ CH ₂ CN | 2,4-Me ₂ -Ph | |

| | | | | |
|----|-----|--------------------|---|-------------------------|
| | 621 | C-OH | NHCH(Et) ₂ | 2,4-Me ₂ -Ph |
| | 623 | C-OH | N(CH ₂ CH ₂ OMe) ₂ | 2,4-Me ₂ -Ph |
| | 624 | C-NEt ₂ | NHCH(CH ₂ OMe) ₂ | 2,4-Me ₂ -Ph |
| | 625 | C-NEt ₂ | NEt ₂ | 2,4-Me ₂ -Ph |
| 5 | 626 | C-NEt ₂ | N(c-Pr)CH ₂ CH ₂ CN | 2,4-Me ₂ -Ph |
| | 627 | C-NEt ₂ | NHCH(Et) ₂ | 2,4-Me ₂ -Ph |
| | 628 | C-NEt ₂ | N(CH ₂ CH ₂ OMe) ₂ | 2,4-Me ₂ -Ph |
| | 629 | C-Me | NHCH(Et) ₂ | 2-Me-4-CN-Ph |
| 10 | 630 | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Me-4-CN-Ph |

Notes for Table 3:

- a) CI-HRMS: Calcd:367.2610, Found: 367.2607 (M + H);
- b) CI-HRMS: Calcd:384.2400, Found: 384.2393 (M + H);
- 15 c) CI-HRMS: Calcd:404.1853, Found: 404.1844 (M + H);
- d) CI-HRMS: Calcd:381.1594, Found: 381.1596 (M + H);
Analysis: Calcd: C: 63.07, H, 5.57, N, 22.07, Cl, 9.32;
Found: C: 63.40, H, 5.55, N, 21.96, Cl: 9.15
- 20 e) CI-HRMS: Calcd:369.1594, Found: 369.1576 (M + H);
- f) CI-HRMS: Calcd:354.2216, Found: 354.2211 (M + H);
- g) CI-HRMS: Calcd:410.1072, Found: 410.1075 (M + H);
- h) CI-HRMS: Calcd:414.2427, Found: 414.2427 (M + H);
- i) CI-HRMS: Calcd:368.2372, Found: 368.2372 (M + H);
- 25 j) CI-HRMS: Calcd:384.1955, Found: 384.1947 (M + H);
- k) CI-HRMS: Calcd:391.2168, Found: 391.2160 (M + H);
- l) CI-HRMS: Calcd:335.1984, Found: 335.1961 (M + H);
- m) CI-HRMS: Calcd:382.0759, Found: 382.0765 (M + H);
- n) NH₃-CI MS: Calcd: 360, Found: 360 (M + H)+
- 30 o) NH₃-CI MS: Calcd: 374, Found: 374 (M + H)+;
NMR (CDCl₃, 300 MHz) : δ 7.29 (d, J=8.4Hz, 1H), 7.04 (dd, J=1.8,8Hz, 1H), 6.96 (d, J=1.8Hz, 1H), 6.15 (d, J=10, 1H), 4.19 (m, 1H), 3.81 (s, 3H), 2.47 (s, 3H), 2.32 (s, 3H), 1.65 (m, 4H), 0.99 (t, J=7.32Hz, 6H)
- 35 p) NH₃-CI MS: Calcd: 390, Found: 390 (M + H)+;

NMR (CDCl₃, 300 MHz) : δ 7.28 (d, J=8Hz, 1H), 7.03 (d, J=8Hz, 1H), 6.96 (s, 1H), 6.52 (d, J=9Hz, 1H), 4.36 (m, 1H), 3.8 (s, 3H), 3.55 (m, 2H), 3.39 (s, 3H), 2.47 (s, 3H), 2.32 (s, 3H), 1.76 (m, 2H), 1.01 (t, J=7.32Hz, 3H).

- q) CI-HRMS: Calcd: 354.2294, Found: 354.2279 (M + H)⁺
 r) CI-HRMS: Calcd: 340.2137, Found: 340.2138 (M + H)⁺
 s) CI-HRMS: Calcd: 436.1307, Found: 436.1296 (M + H)⁺

10

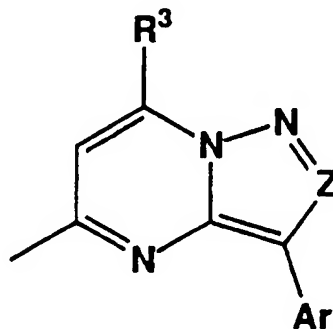
The examples delineated in TABLE 4 may be prepared by the methods outlined in Examples 1A, 1B, 432, 433, 434.

Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is

15 Example, EtOAc is ethyl acetate.

TABLE 4

20



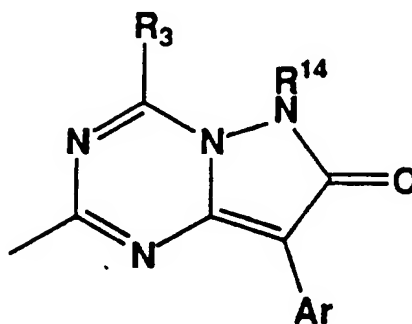
| 25 | Ex. | Z | R ₃ | Ar | mp (°C) |
|----|-----|------|---|--------------------------------|---------|
| | 631 | C-Me | NHCH(Et) ₂ | 2-Br-4,5-(MeO) ₂ Ph | 160-161 |
| | 632 | C-Me | NHCH(Et) ₂ | 2-Br-4-MeOPh | 110-111 |
| | 633 | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Br-4-MeOPh | 74-76 |
| | 634 | C-Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4-MeOPh | 128-130 |

| | | | | | |
|----|-----|--------------------|---|---------------------------------|---------|
| | 635 | C-Me | N(Et) ₂ | 2-Me-4-ClPh | 113-114 |
| | 636 | C-Me | N(c-Pr)Et | 2,4-Cl ₂ Ph | |
| | 637 | C-Me | N(c-Pr)Et | 2,4-Me ₂ Ph | |
| | 638 | C-Me | N(c-Pr)Et | 2,4,6-Me ₃ Ph | |
| 5 | 639 | C-Me | N(c-Pr)Et | 2-Me-4-MeOPh | |
| | 640 | C-Me | N(c-Pr)Et | 2-Cl-4-MeOPh | |
| | 641 | C-Me | N(c-Pr)Et | 2-Cl-4-MePh | |
| | 642 | C-Me | N(c-Pr)Et | 2-Me-4-ClPh | |
| 10 | 643 | C-Me | NHCH(c-Pr) ₂ | 2,4-Cl ₂ -Ph | |
| | 644 | C-Me | NHCH(c-Pr) ₂ | 2,4-Me ₂ -Ph | |
| | 645 | C-Me | NHCH(c-Pr) ₂ | 2-Me-4-Cl-Ph | |
| | 646 | C-Me | NHCH(c-Pr) ₂ | 2-Cl-4-Me-Ph | |
| | 647 | C-Me | NHCH(c-Pr) ₂ | 2-Me-4-OMe-Ph | |
| | 648 | C-Me | NHCH(c-Pr) ₂ | 2-Cl-4-OMe-Ph | |
| 15 | 649 | C-Me | NHCH(CH ₂ OMe) ₂ | 2-Cl-5-F-OMePh | |
| | 650 | C-Me | NEt ₂ | 2-Cl-5-F-OMePh | |
| | 651 | C-Me | N(c-Pr)CH ₂ CH ₂ CN | 2-Cl-5-F-OMePh | |
| | 652 | C-Me | NHCH(Et) ₂ | 2-Cl-5-F-OMePh | |
| | 653 | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Cl-5-F-OMePh | |
| 20 | 654 | C-Me | NEt ₂ | 2,6-Me ₂ -pyrid-3-yl | |
| | 655 | C-Me | N(c-Pr)CH ₂ CH ₂ CN | 2,6-Me ₂ -pyrid-3-yl | |
| | 656 | C-Me | NHCH(Et) ₂ | 2,6-Me ₂ -pyrid-3-yl | |
| | 657 | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2,6-Me ₂ -pyrid-3-yl | |
| | 658 | C-OH | NHCH(CH ₂ OMe) ₂ | 2,4-Me ₂ -Ph | |
| 25 | 659 | C-OH | NEt ₂ | 2,4-Me ₂ -Ph | |
| | 660 | C-OH | N(c-Pr)CH ₂ CH ₂ CN | 2,4-Me ₂ -Ph | |
| | 661 | C-OH | NHCH(Et) ₂ | 2,4-Me ₂ -Ph | |
| | 662 | C-OH | N(CH ₂ CH ₂ OMe) ₂ | 2,4-Me ₂ -Ph | |
| | 663 | C-NEt ₂ | NHCH(CH ₂ OMe) ₂ | 2,4-Me ₂ -Ph | |
| 30 | 664 | C-NEt ₂ | NEt ₂ | 2,4-Me ₂ -Ph | |
| | 665 | C-NEt ₂ | N(c-Pr)CH ₂ CH ₂ CN | 2,4-Me ₂ -Ph | |
| | 666 | C-NEt ₂ | NHCH(Et) ₂ | 2,4-Me ₂ -Ph | |
| | 667 | C-NEt ₂ | N(CH ₂ CH ₂ OMe) ₂ | 2,4-Me ₂ -Ph | |
| | 668 | C-Me | NHCH(Et) ₂ | 2-Me-4-CN-Ph | |
| 35 | 669 | C-Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Me-4-CN-Ph | |

The examples in Tables 5 or 6 may be prepared by the methods illustrated in Examples 1A, 1B, 2, 3, 6, 431, 432, 433, 434 or by appropriate combinations thereof. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example.

10

Table 5



15

| Ex. | R ₁₄ | R ₃ | Ar |
|--------|-----------------|--|-------------------------|
| 670 | Me | NHCH(CH ₂ OMe) ₂ | 2,4-Cl ₂ -Ph |
| 671 | Me | NHCHPr ₂ | 2,4-Cl ₂ -Ph |
| 672 | Me | NEtBu | 2,4-Cl ₂ -Ph |
| 20 673 | Me | NPr(CH ₂ -c-C ₃ H ₅) | 2,4-Cl ₂ -Ph |
| 674 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2,4-Cl ₂ -Ph |
| 675 | Me | NH-3-heptyl | 2,4-Cl ₂ -Ph |
| 676 | Me | NHCH(Et)CH ₂ OMe | 2,4-Cl ₂ -Ph |
| 677 | Me | NEt ₂ | 2,4-Cl ₂ -Ph |
| 25 678 | Me | NHCH(CH ₂ OEt) ₂ | 2,4-Cl ₂ -Ph |
| 679 | Me | NH-3-pentyl | 2,4-Cl ₂ -Ph |
| 680 | Me | NMePh | 2,4-Cl ₂ -Ph |
| 681 | Me | NPr ₂ | 2,4-Cl ₂ -Ph |
| 682 | Me | NH-3-hexyl | 2,4-Cl ₂ -Ph |
| 30 683 | Me | morpholino | 2,4-Cl ₂ -Ph |

| | | | | |
|----|-----|----|--|---------------------------|
| | 684 | Me | N(CH ₂ Ph)CH ₂ CH ₂ OMe | 2,4-Cl ₂ -Ph |
| | 685 | Me | NHCH(CH ₂ Ph)CH ₂ OMe | 2,4-Cl ₂ -Ph |
| | 686 | Me | NH-4-tetrahydropyranyl | 2,4-Cl ₂ -Ph |
| | 687 | Me | NH-cyclopentyl | 2,4-Cl ₂ -Ph |
| 5 | 688 | Me | OEt | 2,4-Cl ₂ -Ph |
| | 689 | Me | OCH(Et)CH ₂ OMe | 2,4-Cl ₂ -Ph |
| | 690 | Me | OCH ₂ Ph | 2,4-Cl ₂ -Ph |
| | 691 | Me | O-3-pentyl | 2,4-Cl ₂ -Ph |
| | 692 | Me | SEt | 2,4-Cl ₂ -Ph |
| 10 | 693 | Me | S(O)Et | 2,4-Cl ₂ -Ph |
| | 694 | Me | SO ₂ Et | 2,4-Cl ₂ -Ph |
| | 695 | Me | Ph | 2,4-Cl ₂ -Ph |
| | 696 | Me | 2-CF ₃ -Ph | 2,4-Cl ₂ -Ph |
| | 697 | Me | 2-Ph-Ph | 2,4-Cl ₂ -Ph |
| 15 | 698 | Me | 3-pentyl | 2,4-Cl ₂ -Ph |
| | 699 | Me | cyclobutyl | 2,4-Cl ₂ -Ph |
| | 700 | Me | 3-pyridyl | 2,4-Cl ₂ -Ph |
| | 701 | Me | CH(Et)CH ₂ CONMe ₂ | 2,4-Cl ₂ -Ph |
| | 702 | Me | CH(Et)CH ₂ CH ₂ NMe ₂ | 2,4-Cl ₂ -Ph |
| 20 | 703 | Me | NHCH(CH ₂ OMe) ₂ | 2,4,6-Me ₃ -Ph |
| | 704 | Me | NHCHPr ₂ | 2,4,6-Me ₃ -Ph |
| | 705 | Me | NEtBu | 2,4,6-Me ₃ -Ph |
| | 706 | Me | NPr(CH ₂ -c-C ₃ H ₅) | 2,4,6-Me ₃ -Ph |
| | 707 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2,4,6-Me ₃ -Ph |
| 25 | 708 | Me | NH-3-heptyl | 2,4,6-Me ₃ -Ph |
| | 709 | Me | NHCH(Et)CH ₂ OMe | 2,4,6-Me ₃ -Ph |
| | 710 | Me | NEt ₂ | 2,4,6-Me ₃ -Ph |
| | 711 | Me | NHCH(CH ₂ OEt) ₂ | 2,4,6-Me ₃ -Ph |
| | 712 | Me | NH-3-pentyl | 2,4,6-Me ₃ -Ph |
| 30 | 713 | Me | NMePh | 2,4,6-Me ₃ -Ph |
| | 714 | Me | NPr ₂ | 2,4,6-Me ₃ -Ph |
| | 715 | Me | NH-3-hexyl | 2,4,6-Me ₃ -Ph |
| | 716 | Me | morpholino | 2,4,6-Me ₃ -Ph |
| | 717 | Me | N(CH ₂ Ph)CH ₂ CH ₂ OMe | 2,4,6-Me ₃ -Ph |
| 35 | 718 | Me | NHCH(CH ₂ Ph)CH ₂ OMe | 2,4,6-Me ₃ -Ph |
| | 719 | Me | NH-4-tetrahydropyranyl | 2,4,6-Me ₃ -Ph |

| | | | | |
|----|-----|----|---|-----------------------------|
| | 720 | Me | NH-cyclopentyl | 2, 4, 6-Me ₃ -Ph |
| | 721 | Me | OEt | 2, 4, 6-Me ₃ -Ph |
| | 722 | Me | OCH(Et)CH ₂ OMe | 2, 4, 6-Me ₃ -Ph |
| | 723 | Me | OCH ₂ Ph | 2, 4, 6-Me ₃ -Ph |
| 5 | 724 | Me | O-3-pentyl | 2, 4, 6-Me ₃ -Ph |
| | 725 | Me | SEt | 2, 4, 6-Me ₃ -Ph |
| | 726 | Me | S(O)Et | 2, 4, 6-Me ₃ -Ph |
| | 727 | Me | SO ₂ Et | 2, 4, 6-Me ₃ -Ph |
| | 728 | Me | CH(CO ₂ Et) ₂ | 2, 4, 6-Me ₃ -Ph |
| 10 | 729 | Me | C(Et)(CO ₂ Et) ₂ | 2, 4, 6-Me ₃ -Ph |
| | 730 | Me | CH(Et)CH ₂ OH | 2, 4, 6-Me ₃ -Ph |
| | 731 | Me | CH(Et)CH ₂ OMe | 2, 4, 6-Me ₃ -Ph |
| | 732 | Me | CONMe ₂ | 2, 4, 6-Me ₃ -Ph |
| | 733 | Me | COCH ₃ | 2, 4, 6-Me ₃ -Ph |
| 15 | 734 | Me | CH(OH)CH ₃ | 2, 4, 6-Me ₃ -Ph |
| | 735 | Me | C(OH)Ph-3-pyridyl | 2, 4, 6-Me ₃ -Ph |
| | 736 | Me | Ph | 2, 4, 6-Me ₃ -Ph |
| | 737 | Me | 2-Ph-Ph | 2, 4, 6-Me ₃ -Ph |
| | 738 | Me | 3-pentyl | 2, 4, 6-Me ₃ -Ph |
| 20 | 739 | Me | cyclobutyl | 2, 4, 6-Me ₃ -Ph |
| | 740 | Me | 3-pyridyl | 2, 4, 6-Me ₃ -Ph |
| | 741 | Me | CH(Et)CH ₂ CONMe ₂ | 2, 4, 6-Me ₃ -Ph |
| | 742 | Me | CH(Et)CH ₂ CH ₂ NMe ₂ | 2, 4, 6-Me ₃ -Ph |
| | 743 | Me | NHCH(CH ₂ OMe) ₂ | 2, 4-Me ₂ -Ph |
| 25 | 744 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2, 4-Me ₂ -Ph |
| | 745 | Me | NHCH(Et)CH ₂ OMe | 2, 4-Me ₂ -Ph |
| | 746 | Me | NH-3-pentyl | 2, 4-Me ₂ -Ph |
| | 747 | Me | NEt ₂ | 2, 4-Me ₂ -Ph |
| | 748 | Me | N(CH ₂ CN) ₂ | 2, 4-Me ₂ -Ph |
| 30 | 749 | Me | NHCH(Me)CH ₂ OMe | 2, 4-Me ₂ -Ph |
| | 750 | Me | OCH(Et)CH ₂ OMe | 2, 4-Me ₂ -Ph |
| | 751 | Me | NPr-c-C ₃ H ₅ | 2, 4-Me ₂ -Ph |
| | 752 | Me | NHCH(Me)CH ₂ NMe ₂ | 2, 4-Me ₂ -Ph |
| | 753 | Me | N(c-C ₃ H ₅)CH ₂ CH ₂ CN | 2, 4-Me ₂ -Ph |
| 35 | 754 | Me | N(Pr)CH ₂ CH ₂ CN | 2, 4-Me ₂ -Ph |
| | 755 | Me | N(Bu)CH ₂ CH ₂ CN | 2, 4-Me ₂ -Ph |

| | | | | |
|----|-----|----|--|-----------------------------|
| | 756 | Me | NHCHPr ₂ | 2,4-Me ₂ -Ph |
| | 757 | Me | NEtBu | 2,4-Me ₂ -Ph |
| | 758 | Me | NPr(CH ₂ -c-C ₃ H ₅) | 2,4-Me ₂ -Ph |
| | 759 | Me | NH-3-heptyl | 2,4-Me ₂ -Ph |
| 5 | 760 | Me | NEt ₂ | 2,4-Me ₂ -Ph |
| | 761 | Me | NHCH(CH ₂ OEt) ₂ | 2,4-Me ₂ -Ph |
| | 762 | Me | NH-3-pentyl | 2,4-Me ₂ -Ph |
| | 763 | Me | NMePh | 2,4-Me ₂ -Ph |
| | 764 | Me | NPr ₂ | 2,4-Me ₂ -Ph |
| 10 | 765 | Me | NH-3-hexyl | 2,4-Me ₂ -Ph |
| | 766 | Me | morpholino | 2,4-Me ₂ -Ph |
| | 767 | Me | N(CH ₂ Ph)CH ₂ CH ₂ OMe | 2,4-Me ₂ -Ph |
| | 768 | Me | NHCH(CH ₂ Ph)CH ₂ OMe | 2,4-Me ₂ -Ph |
| | 769 | Me | NH-4-tetrahydropyranyl | 2,4-Me ₂ -Ph |
| 15 | 770 | Me | NH-cyclopentyl | 2,4-Me ₂ -Ph |
| | 771 | Me | NHCH(CH ₂ OMe) ₂ | 2-Me-4-MeO-Ph |
| | 772 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Me-4-MeO-Ph |
| | 773 | Me | NHCH(Et)CH ₂ OMe | 2-Me-4-MeO-Ph |
| | 774 | Me | N(Pr)CH ₂ CH ₂ CN | 2-Me-4-MeO-Ph |
| 20 | 775 | Me | OCH(Et)CH ₂ OMe | 2-Me-4-MeO-Ph |
| | 776 | Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4-MeO-Ph |
| | 777 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Br-4-MeO-Ph |
| | 778 | Me | NHCH(Et)CH ₂ OMe | 2-Br-4-MeO-Ph |
| | 779 | Me | N(Pr)CH ₂ CH ₂ CN | 2-Br-4-MeO-Ph |
| 25 | 780 | Me | OCH(Et)CH ₂ OMe | 2-Br-4-MeO-Ph |
| | 781 | Me | NHCH(CH ₂ OMe) ₂ | 2-Me-4-NMe ₂ -Ph |
| | 782 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Me-4-NMe ₂ -Ph |
| | 783 | Me | NHCH(Et)CH ₂ OMe | 2-Me-4-NMe ₂ -Ph |
| | 784 | Me | N(Pr)CH ₂ CH ₂ CN | 2-Me-4-NMe ₂ -Ph |
| 30 | 785 | Me | OCH(Et)CH ₂ OMe | 2-Me-4-NMe ₂ -Ph |
| | 786 | Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4-NMe ₂ -Ph |
| | 787 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Br-4-NMe ₂ -Ph |
| | 788 | Me | NHCH(Et)CH ₂ OMe | 2-Br-4-NMe ₂ -Ph |
| | 789 | Me | N(Pr)CH ₂ CH ₂ CN | 2-Br-4-NMe ₂ -Ph |
| 35 | 790 | Me | OCH(Et)CH ₂ OMe | 2-Br-4-NMe ₂ -Ph |
| | 791 | Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4-i-Pr-Ph |

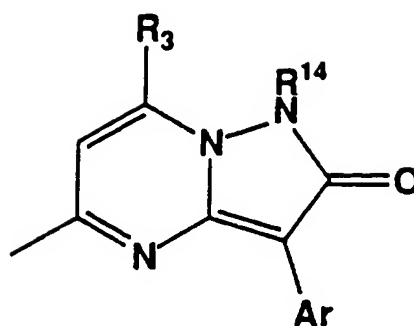
| | | | | |
|----|-----|----|---|-----------------------------------|
| | 792 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Br-4-i-Pr-Ph |
| | 793 | Me | NHCH(Et)CH ₂ OMe | 2-Br-4-i-Pr-Ph |
| | 794 | Me | N(Pr)CH ₂ CH ₂ CN | 2-Br-4-i-Pr-Ph |
| | 795 | Me | OCH(Et)CH ₂ OMe | 2-Br-4-i-Pr-Ph |
| 5 | 796 | Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4-Me-Ph |
| | 797 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Br-4-Me-Ph |
| | 798 | Me | NHCH(Et)CH ₂ OMe | 2-Br-4-Me-Ph |
| | 799 | Me | N(Pr)CH ₂ CH ₂ CN | 2-Br-4-Me-Ph |
| | 800 | Me | OCH(Et)CH ₂ OMe | 2-Br-4-Me-Ph |
| 10 | 801 | Me | NHCH(CH ₂ OMe) ₂ | 2-Me-4-Br-Ph |
| | 802 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Me-4-Br-Ph |
| | 803 | Me | NHCH(Et)CH ₂ OMe | 2-Me-4-Br-Ph |
| | 804 | Me | N(Pr)CH ₂ CH ₂ CN | 2-Me-4-Br-Ph |
| | 805 | Me | OCH(Et)CH ₂ OMe | 2-Me-4-Br-Ph |
| 15 | 806 | Me | NHCH(CH ₂ OMe) ₂ | 2-Cl-4,6-Me ₂ -Ph |
| | 807 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Cl-4,6-Me ₂ -Ph |
| | 808 | Me | NHCH(CH ₂ OMe) ₂ | 4-Br-2,6-(Me) ₂ -Ph |
| | 809 | Me | N(CH ₂ CH ₂ OMe) ₂ | 4-Br-2,6-(Me) ₂ -Ph |
| | 810 | Me | NHCH(CH ₂ OMe) ₂ | 4-i-Pr-2-SMe-Ph |
| 20 | 811 | Me | N(CH ₂ CH ₂ OMe) ₂ | 4-i-Pr-2-SMe-Ph |
| | 812 | Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4-CF ₃ -Ph |
| | 813 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Br-4-CF ₃ -Ph |
| | 814 | Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4,6-(MeO) ₂ -Ph |
| | 815 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Br-4,6-(MeO) ₂ -Ph |
| 25 | 816 | Me | NHCH(CH ₂ OMe) ₂ | 2-Cl-4,6-(MeO) ₂ -Ph |
| | 817 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Cl-4,6-(MeO) ₂ -Ph |
| | 818 | Me | NHCH(CH ₂ OMe) ₂ | 2,6-(Me) ₂ -4-SMe-Ph |
| | 819 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2,6-(Me) ₂ -4-SMe-Ph |
| | 820 | Me | NHCH(CH ₂ OMe) ₂ | 4-(COMe)-2-Br-Ph |
| 30 | 821 | Me | N(CH ₂ CH ₂ OMe) ₂ | 4-(COMe)-2-Br-Ph |
| | 822 | Me | NHCH(CH ₂ OMe) ₂ | 2,4,6-Me ₃ -pyrid-3-yl |
| | 823 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2,4,6-Me ₃ -pyrid-3-yl |
| | 824 | Me | NHCH(CH ₂ OMe) ₂ | 2,4-(Br) ₂ -Ph |
| | 825 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2,4-(Br) ₂ -Ph |
| 35 | 826 | Me | NHCH(CH ₂ OMe) ₂ | 4-i-Pr-2-SMe-Ph |
| | 827 | Me | N(CH ₂ CH ₂ OMe) ₂ | 4-i-Pr-2-SMe-Ph |

| | | | | |
|----|-----|----|---|--|
| | 828 | Me | NHCH(CH ₂ OMe) ₂ | 4-i-Pr-2-SO ₂ Me-Ph |
| | 829 | Me | N(CH ₂ CH ₂ OMe) ₂ | 4-i-Pr-2-SO ₂ Me-Ph |
| | 830 | Me | NHCH(CH ₂ OMe) ₂ | 2,6-(Me) ₂ -4-SMe-Ph |
| | 831 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2,6-(Me) ₂ -4-SMe-Ph |
| 5 | 832 | Me | NHCH(CH ₂ OMe) ₂ | 2,6-(Me) ₂ -4-SO ₂ Me-Ph |
| | 833 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2,6-(Me) ₂ -4-SO ₂ Me-Ph |
| | 834 | Me | NHCH(CH ₂ OMe) ₂ | 2-I-4-i-Pr-Ph |
| | 835 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-I-4-i-Pr-Ph |
| | 836 | Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4-N(Me) ₂ -6-MeO-Ph |
| 10 | 837 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Br-4-N(Me) ₂ -6-MeO-Ph |
| | 838 | Me | NEt ₂ | 2-Br-4-MeO-Ph |
| | 839 | Me | NH-3-pentyl | 2-Br-4-MeO-Ph |
| | 840 | Me | NHCH(CH ₂ OMe) ₂ | 2-CN-4-Me-Ph |
| | 841 | Me | N(c-C ₃ H ₅)CH ₂ CH ₂ CN | 2,4,6-Me ₃ -Ph |
| 15 | 842 | Me | NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe | 2-Me-4-Br-Ph |
| | 843 | Me | NHCH(CH ₂ OMe) ₂ | 2,5-Me ₂ -4-MeO-Ph |
| | 844 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2,5-Me ₂ -4-MeO-Ph |
| | 845 | Me | NH-3-pentyl | 2,5-Me ₂ -4-MeO-Ph |
| | 846 | Me | NEt ₂ | 2,5-Me ₂ -4-MeO-Ph |
| 20 | 847 | Me | NHCH(CH ₂ OMe) ₂ | 2-Cl-4-MePh |
| | 848 | Me | NCH(Et)CH ₂ OMe | 2-Cl-4-MePh |
| | 849 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Cl-4-MePh |
| | 850 | Me | (S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe | 2-Cl-4-MePh |
| | 851 | Me | N(c-C ₃ H ₅)CH ₂ CH ₂ CN | 2,5-Me ₂ -4-MeOPh |
| 25 | 852 | Me | NEt ₂ | 2-Me-4-MeOPh |
| | 853 | Me | OEt | 2-Me-4-MeOPh |
| | 854 | Me | (S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe | 2-Me-4-MeOPh |
| | 855 | Me | N(c-C ₃ H ₅)CH ₂ CH ₂ CN | 2-Me-4-MeOPh |
| | 856 | Me | NHCH(CH ₂ CH ₂ OEt) ₂ | 2-Me-4-MeOPh |
| 30 | 857 | Me | N(c-C ₃ H ₅)CH ₂ CH ₂ CN | 2,4-Cl ₂ -Ph |
| | 858 | Me | NEt ₂ | 2-Me-4-ClPh |
| | 859 | Me | NH-3-pentyl | 2-Me-4-ClPh |
| | 860 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Me-4-ClPh |
| | 861 | Me | NHCH(CH ₂ OMe) ₂ | 2-Me-4-ClPh |
| 35 | 862 | Me | NEt ₂ | 2-Me-4-ClPh |
| | 863 | Me | NEt ₂ | 2-Cl-4-MePh |

| | | | | |
|----|-----|----|---|--------------------------------|
| | 864 | Me | NH-3-pentyl | 2-Cl-4-MePh |
| | 865 | Me | NHCH(CH ₂ OMe) ₂ | 2-Cl-4-MeOPh |
| | 866 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Cl-4-MeOPh |
| | 867 | Me | NHCH(Et)CH ₂ OMe | 2-Cl-4-MeOPh |
| 5 | 868 | Me | N(c-Pr)CH ₂ CH ₂ CN | 2-Cl-4-MeOPh |
| | 869 | Me | NEt ₂ | 2-Cl-4-MeOPh |
| | 870 | Me | NH-3-pentyl | 2-Cl-4-MeOPh |
| | 871 | Me | NHCH(Et)CH ₂ CH ₂ OMe | 2-Cl-4-MeOPh |
| | 872 | Me | NHCH(Me)CH ₂ CH ₂ OMe | 2-Cl-4-MeOPh |
| 10 | 873 | Me | NHCH(Et)CH ₂ CH ₂ OMe | 2-Br-4-MeOPh |
| | 874 | Me | NHCH(Me)CH ₂ CH ₂ OMe | 2-Br-4-MeOPh |
| | 875 | Me | NHCH(Et)CH ₂ CH ₂ OMe | 2-Me-4-MeOPh |
| | 876 | Me | NHCH(Me)CH ₂ CH ₂ OMe | 2-Me-4-MeOPh |
| | 877 | Me | NHCH(CH ₂ OMe) ₂ | 2-Cl-4,5-(MeO) ₂ Ph |
| 15 | 878 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Cl-4,5-(MeO) ₂ Ph |
| | 879 | Me | NHCH(Et)CH ₂ OMe | 2-Cl-4,5-(MeO) ₂ Ph |
| | 880 | Me | N(c-Pr)CH ₂ CH ₂ CN | 2-Cl-4,5-(MeO) ₂ Ph |
| | 881 | Me | NEt ₂ | 2-Cl-4,5-(MeO) ₂ Ph |
| | 882 | Me | NH-3-pentyl | 2-Cl-4,5-(MeO) ₂ Ph |
| 20 | 883 | Me | NHCH(Et)CH ₂ CH ₂ OMe | 2-Cl-4,5-(MeO) ₂ Ph |
| | 884 | Me | NHCH(Me)CH ₂ CH ₂ OMe | 2-Cl-4,5-(MeO) ₂ Ph |
| | 885 | Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4,5-(MeO) ₂ Ph |
| | 886 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Br-4,5-(MeO) ₂ Ph |
| | 887 | Me | NHCH(Et)CH ₂ OMe | 2-Br-4,5-(MeO) ₂ Ph |
| 25 | 888 | Me | N(c-Pr)CH ₂ CH ₂ CN | 2-Br-4,5-(MeO) ₂ Ph |
| | 889 | Me | NEt ₂ | 2-Br-4,5-(MeO) ₂ Ph |
| | 890 | Me | NH-3-pentyl | 2-Br-4,5-(MeO) ₂ Ph |
| | 891 | Me | NHCH(CH ₂ OMe) ₂ | 2-Cl-4,6-(MeO) ₂ Ph |
| | 892 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Cl-4,6-(MeO) ₂ Ph |
| 30 | 893 | Me | NEt ₂ | 2-Cl-4,6-(MeO) ₂ Ph |
| | 894 | Me | NH-3-pentyl | 2-Cl-4,6-(MeO) ₂ Ph |
| | 895 | Me | NHCH(CH ₂ OMe) ₂ | 2-Me-4,6-(MeO) ₂ Ph |
| | 896 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Me-4,6-(MeO) ₂ Ph |
| | 897 | Me | NHCH(Et)CH ₂ OMe | 2-Me-4,6-(MeO) ₂ Ph |
| 35 | 898 | Me | NEt ₂ | 2-Me-4,6-(MeO) ₂ Ph |
| | 899 | Me | NH-3-pentyl | 2-Me-4,6-(MeO) ₂ Ph |

| | | | | |
|----|-----|----|--|--------------|
| | 900 | Me | NHCH (Et) CH ₂ CH ₂ OMe | 2-Me-4-MeOPh |
| | 901 | Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-Me-4-MeOPh |
| | 902 | Me | NHCH (CH ₂ OMe) ₂ | 2-MeO-4-MePh |
| | 903 | Me | N (CH ₂ CH ₂ OMe) ₂ | 2-MeO-4-MePh |
| 5 | 904 | Me | NHCH (Et) CH ₂ OMe | 2-MeO-4-MePh |
| | 905 | Me | N (c-Pr) CH ₂ CH ₂ CN | 2-MeO-4-MePh |
| | 906 | Me | NEt ₂ | 2-MeO-4-MePh |
| | 907 | Me | NH-3-pentyl | 2-MeO-4-MePh |
| | 908 | Me | NHCH (Et) CH ₂ CH ₂ OMe | 2-MeO-4-MePh |
| 10 | 909 | Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-MeO-4-MePh |
| | 910 | Me | NHCH (CH ₂ OMe) ₂ | 2-MeO-4-MePh |
| | 911 | Me | N (CH ₂ CH ₂ OMe) ₂ | 2-MeO-4-MePh |
| | 912 | Me | NHCH (Et) CH ₂ OMe | 2-MeO-4-MePh |
| | 913 | Me | N (c-Pr) CH ₂ CH ₂ CN | 2-MeO-4-MePh |
| 15 | 914 | Me | NEt ₂ | 2-MeO-4-MePh |
| | 915 | Me | NH-3-pentyl | 2-MeO-4-MePh |
| | 916 | Me | NHCH (CH ₂ OMe) ₂ | 2-MeO-4-ClPh |
| | 917 | Me | N (CH ₂ CH ₂ OMe) ₂ | 2-MeO-4-ClPh |
| | 918 | Me | NHCH (Et) CH ₂ OMe | 2-MeO-4-ClPh |
| 20 | 919 | Me | NEt ₂ | 2-MeO-4-ClPh |
| | 920 | Me | NH-3-pentyl | 2-MeO-4-ClPh |

Table 6



| 5 | Ex. | R ₁₄ | R ₃ | Ar |
|----|-----|-----------------|--|-------------------------|
| | 921 | Me | NHCH(CH ₂ OMe) ₂ | 2,4-Cl ₂ -Ph |
| | 922 | Me | NHCHPr ₂ | 2,4-Cl ₂ -Ph |
| | 923 | Me | NEtBu | 2,4-Cl ₂ -Ph |
| 10 | 924 | Me | NPr(CH ₂ -c-C ₃ H ₅) | 2,4-Cl ₂ -Ph |
| | 925 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2,4-Cl ₂ -Ph |
| | 926 | Me | NH-3-heptyl | 2,4-Cl ₂ -Ph |
| | 927 | Me | NHCH(Et)CH ₂ OMe | 2,4-Cl ₂ -Ph |
| | 928 | Me | NEt ₂ | 2,4-Cl ₂ -Ph |
| 15 | 929 | Me | NHCH(CH ₂ OEt) ₂ | 2,4-Cl ₂ -Ph |
| | 930 | Me | NH-3-pentyl | 2,4-Cl ₂ -Ph |
| | 931 | Me | NMePh | 2,4-Cl ₂ -Ph |
| | 932 | Me | NPr ₂ | 2,4-Cl ₂ -Ph |
| | 933 | Me | NH-3-hexyl | 2,4-Cl ₂ -Ph |
| 20 | 934 | Me | morpholino | 2,4-Cl ₂ -Ph |
| | 935 | Me | N(CH ₂ Ph)CH ₂ CH ₂ OMe | 2,4-Cl ₂ -Ph |
| | 936 | Me | NHCH(CH ₂ Ph)CH ₂ OMe | 2,4-Cl ₂ -Ph |
| | 937 | Me | NH-4-tetrahydropyranyl | 2,4-Cl ₂ -Ph |
| | 938 | Me | NH-cyclopentyl | 2,4-Cl ₂ -Ph |
| 25 | 939 | Me | OEt | 2,4-Cl ₂ -Ph |
| | 940 | Me | OCH(Et)CH ₂ OMe | 2,4-Cl ₂ -Ph |
| | 941 | Me | OCH ₂ Ph | 2,4-Cl ₂ -Ph |
| | 942 | Me | O-3-pentyl | 2,4-Cl ₂ -Ph |
| | 943 | Me | SEt | 2,4-Cl ₂ -Ph |

| | | | | |
|----|-----|----|--|---------------------------|
| | 944 | Me | S(O)Et | 2,4-Cl ₂ -Ph |
| | 945 | Me | SO ₂ Et | 2,4-Cl ₂ -Ph |
| | 946 | Me | Ph | 2,4-Cl ₂ -Ph |
| | 947 | Me | 2-CF ₃ -Ph | 2,4-Cl ₂ -Ph |
| 5 | 948 | Me | 2-Ph-Ph | 2,4-Cl ₂ -Ph |
| | 949 | Me | 3-pentyl | 2,4-Cl ₂ -Ph |
| | 950 | Me | cyclobutyl | 2,4-Cl ₂ -Ph |
| | 951 | Me | 3-pyridyl | 2,4-Cl ₂ -Ph |
| | 952 | Me | CH(Et)CH ₂ CONMe ₂ | 2,4-Cl ₂ -Ph |
| 10 | 953 | Me | CH(Et)CH ₂ CH ₂ NMe ₂ | 2,4-Cl ₂ -Ph |
| | 954 | Me | NHCH(CH ₂ OMe) ₂ | 2,4,6-Me ₃ -Ph |
| | 955 | Me | NHCHPr ₂ | 2,4,6-Me ₃ -Ph |
| | 956 | Me | NEtBu | 2,4,6-Me ₃ -Ph |
| | 957 | Me | NPr(CH ₂ -c-C ₃ H ₅) | 2,4,6-Me ₃ -Ph |
| 15 | 958 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2,4,6-Me ₃ -Ph |
| | 959 | Me | NH-3-heptyl | 2,4,6-Me ₃ -Ph |
| | 960 | Me | NHCH(Et)CH ₂ OMe | 2,4,6-Me ₃ -Ph |
| | 961 | Me | NEt ₂ | 2,4,6-Me ₃ -Ph |
| | 962 | Me | NHCH(CH ₂ OEt) ₂ | 2,4,6-Me ₃ -Ph |
| 20 | 963 | Me | NH-3-pentyl | 2,4,6-Me ₃ -Ph |
| | 964 | Me | NMePh | 2,4,6-Me ₃ -Ph |
| | 965 | Me | NPr ₂ | 2,4,6-Me ₃ -Ph |
| | 966 | Me | NH-3-hexyl | 2,4,6-Me ₃ -Ph |
| | 967 | Me | morpholino | 2,4,6-Me ₃ -Ph |
| 25 | 968 | Me | N(CH ₂ Ph)CH ₂ CH ₂ OMe | 2,4,6-Me ₃ -Ph |
| | 969 | Me | NHCH(CH ₂ Ph)CH ₂ OMe | 2,4,6-Me ₃ -Ph |
| | 970 | Me | NH-4-tetrahydropyranyl | 2,4,6-Me ₃ -Ph |
| | 971 | Me | NH-cyclopentyl | 2,4,6-Me ₃ -Ph |
| | 972 | Me | OEt | 2,4,6-Me ₃ -Ph |
| 30 | 973 | Me | OCH(Et)CH ₂ OMe | 2,4,6-Me ₃ -Ph |
| | 974 | Me | OCH ₂ Ph | 2,4,6-Me ₃ -Ph |
| | 975 | Me | O-3-pentyl | 2,4,6-Me ₃ -Ph |
| | 976 | Me | SEt | 2,4,6-Me ₃ -Ph |
| | 977 | Me | S(O)Et | 2,4,6-Me ₃ -Ph |
| 35 | 978 | Me | SO ₂ Et | 2,4,6-Me ₃ -Ph |
| | 979 | Me | CH(CO ₂ Et) ₂ | 2,4,6-Me ₃ -Ph |

| | | | | |
|----|------|----|---|---------------------------|
| | 980 | Me | C(Et)(CO ₂ Et) ₂ | 2,4,6-Me ₃ -Ph |
| | 981 | Me | CH(Et)CH ₂ OH | 2,4,6-Me ₃ -Ph |
| | 982 | Me | CH(Et)CH ₂ OMe | 2,4,6-Me ₃ -Ph |
| | 983 | Me | CONMe ₂ | 2,4,6-Me ₃ -Ph |
| 5 | 984 | Me | COCH ₃ | 2,4,6-Me ₃ -Ph |
| | 985 | Me | CH(OH)CH ₃ | 2,4,6-Me ₃ -Ph |
| | 986 | Me | C(OH)Ph-3-pyridyl | 2,4,6-Me ₃ -Ph |
| | 987 | Me | Ph | 2,4,6-Me ₃ -Ph |
| | 988 | Me | 2-Ph-Ph | 2,4,6-Me ₃ -Ph |
| 10 | 989 | Me | 3-pentyl | 2,4,6-Me ₃ -Ph |
| | 990 | Me | cyclobutyl | 2,4,6-Me ₃ -Ph |
| | 991 | Me | 3-pyridyl | 2,4,6-Me ₃ -Ph |
| | 992 | Me | CH(Et)CH ₂ CONMe ₂ | 2,4,6-Me ₃ -Ph |
| | 993 | Me | CH(Et)CH ₂ CH ₂ NMe ₂ | 2,4,6-Me ₃ -Ph |
| 15 | 994 | Me | NHCH(CH ₂ OMe) ₂ | 2,4-Me ₂ -Ph |
| | 995 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2,4-Me ₂ -Ph |
| | 996 | Me | NHCH(Et)CH ₂ OMe | 2,4-Me ₂ -Ph |
| | 997 | Me | NH-3-pentyl | 2,4-Me ₂ -Ph |
| | 998 | Me | NEt ₂ | 2,4-Me ₂ -Ph |
| 20 | 999 | Me | N(CH ₂ CN) ₂ | 2,4-Me ₂ -Ph |
| | 1000 | Me | NHCH(Me)CH ₂ OMe | 2,4-Me ₂ -Ph |
| | 1001 | Me | OCH(Et)CH ₂ OMe | 2,4-Me ₂ -Ph |
| | 1002 | Me | NPr-c-C ₃ H ₅ | 2,4-Me ₂ -Ph |
| | 1003 | Me | NHCH(Me)CH ₂ NMe ₂ | 2,4-Me ₂ -Ph |
| 25 | 1004 | Me | N(c-C ₃ H ₅)CH ₂ CH ₂ CN | 2,4-Me ₂ -Ph |
| | 1005 | Me | N(Pr)CH ₂ CH ₂ CN | 2,4-Me ₂ -Ph |
| | 1006 | Me | N(Bu)CH ₂ CH ₂ CN | 2,4-Me ₂ -Ph |
| | 1007 | Me | NHCHPr ₂ | 2,4-Me ₂ -Ph |
| | 1008 | Me | NEtBu | 2,4-Me ₂ -Ph |
| 30 | 1009 | Me | NPr(CH ₂ -c-C ₃ H ₅) | 2,4-Me ₂ -Ph |
| | 1010 | Me | NH-3-heptyl | 2,4-Me ₂ -Ph |
| | 1011 | Me | NEt ₂ | 2,4-Me ₂ -Ph |
| | 1012 | Me | NHCH(CH ₂ OEt) ₂ | 2,4-Me ₂ -Ph |
| | 1013 | Me | NH-3-pentyl | 2,4-Me ₂ -Ph |
| 35 | 1014 | Me | NMePh | 2,4-Me ₂ -Ph |
| | 1015 | Me | NPr ₂ | 2,4-Me ₂ -Ph |

| | | | | |
|----|------|----|--|-----------------------------|
| | 1016 | Me | NH-3-hexyl | 2,4-Me ₂ -Ph |
| | 1017 | Me | morpholino | 2,4-Me ₂ -Ph |
| | 1018 | Me | N(CH ₂ Ph)CH ₂ CH ₂ OMe | 2,4-Me ₂ -Ph |
| | 1019 | Me | NHCH(CH ₂ Ph)CH ₂ OMe | 2,4-Me ₂ -Ph |
| 5 | 1020 | Me | NH-4-tetrahydropyranyl | 2,4-Me ₂ -Ph |
| | 1021 | Me | NH-cyclopentyl | 2,4-Me ₂ -Ph |
| | 1022 | Me | NHCH(CH ₂ OMe) ₂ | 2-Me-4-MeO-Ph |
| | 1023 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Me-4-MeO-Ph |
| | 1024 | Me | NHCH(Et)CH ₂ OMe | 2-Me-4-MeO-Ph |
| 10 | 1025 | Me | N(Pr)CH ₂ CH ₂ CN | 2-Me-4-MeO-Ph |
| | 1026 | Me | OCH(Et)CH ₂ OMe | 2-Me-4-MeO-Ph |
| | 1027 | Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4-MeO-Ph |
| | 1028 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Br-4-MeO-Ph |
| | 1029 | Me | NHCH(Et)CH ₂ OMe | 2-Br-4-MeO-Ph |
| 15 | 1030 | Me | N(Pr)CH ₂ CH ₂ CN | 2-Br-4-MeO-Ph |
| | 1031 | Me | OCH(Et)CH ₂ OMe | 2-Br-4-MeO-Ph |
| | 1032 | Me | NHCH(CH ₂ OMe) ₂ | 2-Me-4-NMe ₂ -Ph |
| | 1033 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Me-4-NMe ₂ -Ph |
| | 1034 | Me | NHCH(Et)CH ₂ OMe | 2-Me-4-NMe ₂ -Ph |
| 20 | 1035 | Me | N(Pr)CH ₂ CH ₂ CN | 2-Me-4-NMe ₂ -Ph |
| | 1036 | Me | OCH(Et)CH ₂ OMe | 2-Me-4-NMe ₂ -Ph |
| | 1037 | Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4-NMe ₂ -Ph |
| | 1038 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Br-4-NMe ₂ -Ph |
| | 1039 | Me | NHCH(Et)CH ₂ OMe | 2-Br-4-NMe ₂ -Ph |
| 25 | 1040 | Me | N(Pr)CH ₂ CH ₂ CN | 2-Br-4-NMe ₂ -Ph |
| | 1041 | Me | OCH(Et)CH ₂ OMe | 2-Br-4-NMe ₂ -Ph |
| | 1042 | Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4-i-Pr-Ph |
| | 1043 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Br-4-i-Pr-Ph |
| | 1044 | Me | NHCH(Et)CH ₂ OMe | 2-Br-4-i-Pr-Ph |
| 30 | 1045 | Me | N(Pr)CH ₂ CH ₂ CN | 2-Br-4-i-Pr-Ph |
| | 1046 | Me | OCH(Et)CH ₂ OMe | 2-Br-4-i-Pr-Ph |
| | 1047 | Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4-Me-Ph |
| | 1048 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Br-4-Me-Ph |
| | 1049 | Me | NHCH(Et)CH ₂ OMe | 2-Br-4-Me-Ph |
| 35 | 1050 | Me | N(Pr)CH ₂ CH ₂ CN | 2-Br-4-Me-Ph |
| | 1051 | Me | OCH(Et)CH ₂ OMe | 2-Br-4-Me-Ph |

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|----|------|----|---|--|
| | 1052 | Me | NHCH(CH ₂ OMe) ₂ | 2-Me-4-Br-Ph |
| | 1053 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Me-4-Br-Ph |
| | 1054 | Me | NHCH(Et)CH ₂ OMe | 2-Me-4-Br-Ph |
| | 1055 | Me | N(Pr)CH ₂ CH ₂ CN | 2-Me-4-Br-Ph |
| 5 | 1056 | Me | OCH(Et)CH ₂ OMe | 2-Me-4-Br-Ph |
| | 1057 | Me | NHCH(CH ₂ OMe) ₂ | 2-Cl-4,6-Me ₂ -Ph |
| | 1058 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Cl-4,6-Me ₂ -Ph |
| | 1059 | Me | NHCH(CH ₂ OMe) ₂ | 4-Br-2,6-(Me) ₂ -Ph |
| | 1060 | Me | N(CH ₂ CH ₂ OMe) ₂ | 4-Br-2,6-(Me) ₂ -Ph |
| 10 | 1061 | Me | NHCH(CH ₂ OMe) ₂ | 4-i-Pr-2-SMe-Ph |
| | 1062 | Me | N(CH ₂ CH ₂ OMe) ₂ | 4-i-Pr-2-SMe-Ph |
| | 1063 | Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4-CF ₃ -Ph |
| | 1064 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Br-4-CF ₃ -Ph |
| | 1065 | Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4,6-(MeO) ₂ -Ph |
| 15 | 1066 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Br-4,6-(MeO) ₂ -Ph |
| | 1067 | Me | NHCH(CH ₂ OMe) ₂ | 2-Cl-4,6-(MeO) ₂ -Ph |
| | 1068 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-Cl-4,6-(MeO) ₂ -Ph |
| | 1069 | Me | NHCH(CH ₂ OMe) ₂ | 2,6-(Me) ₂ -4-SMe-Ph |
| | 1070 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2,6-(Me) ₂ -4-SMe-Ph |
| 20 | 1071 | Me | NHCH(CH ₂ OMe) ₂ | 4-(COMe)-2-Br-Ph |
| | 1072 | Me | N(CH ₂ CH ₂ OMe) ₂ | 4-(COMe)-2-Br-Ph |
| | 1073 | Me | NHCH(CH ₂ OMe) ₂ | 2,4,6-Me ₃ -pyrid-3-yl |
| | 1074 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2,4,6-Me ₃ -pyrid-3-yl |
| | 1075 | Me | NHCH(CH ₂ OMe) ₂ | 2,4-(Br) ₂ -Ph |
| 25 | 1076 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2,4-(Br) ₂ -Ph |
| | 1077 | Me | NHCH(CH ₂ OMe) ₂ | 4-i-Pr-2-SMe-Ph |
| | 1078 | Me | N(CH ₂ CH ₂ OMe) ₂ | 4-i-Pr-2-SMe-Ph |
| | 1079 | Me | NHCH(CH ₂ OMe) ₂ | 4-i-Pr-2-SO ₂ Me-Ph |
| | 1080 | Me | N(CH ₂ CH ₂ OMe) ₂ | 4-i-Pr-2-SO ₂ Me-Ph |
| 30 | 1081 | Me | NHCH(CH ₂ OMe) ₂ | 2,6-(Me) ₂ -4-SMe-Ph |
| | 1082 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2,6-(Me) ₂ -4-SMe-Ph |
| | 1083 | Me | NHCH(CH ₂ OMe) ₂ | 2,6-(Me) ₂ -4-SO ₂ Me-Ph |
| | 1084 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2,6-(Me) ₂ -4-SO ₂ Me-Ph |
| | 1085 | Me | NHCH(CH ₂ OMe) ₂ | 2-I-4-i-Pr-Ph |
| 35 | 1086 | Me | N(CH ₂ CH ₂ OMe) ₂ | 2-I-4-i-Pr-Ph |
| | 1087 | Me | NHCH(CH ₂ OMe) ₂ | 2-Br-4-N(Me) ₂ -6-MeO-Ph |

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|----|------|----|--|-------------------------------------|
| | 1088 | Me | $N(CH_2CH_2OMe)_2$ | 2-Br-4-N(Me) ₂ -6-MeO-Ph |
| | 1089 | Me | NEt ₂ | 2-Br-4-MeO-Ph |
| | 1090 | Me | NH-3-pentyl | 2-Br-4-MeO-Ph |
| | 1091 | Me | NHCH(CH ₂ OMe) ₂ | 2-CN-4-Me-Ph |
| 5 | 1092 | Me | $N(c-C_3H_5)CH_2CH_2CN$ | 2,4,6-Me ₃ -Ph |
| | 1093 | Me | NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe | 2-Me-4-Br-Ph |
| | 1094 | Me | NHCH(CH ₂ OMe) ₂ | 2,5-Me ₂ -4-MeO-Ph |
| | 1095 | Me | $N(CH_2CH_2OMe)_2$ | 2,5-Me ₂ -4-MeO-Ph |
| | 1096 | Me | NH-3-pentyl | 2,5-Me ₂ -4-MeO-Ph |
| 10 | 1097 | Me | NEt ₂ | 2,5-Me ₂ -4-MeO-Ph |
| | 1098 | Me | NHCH(CH ₂ OMe) ₂ | 2-Cl-4-MePh |
| | 1099 | Me | NCH(Et)CH ₂ OMe | 2-Cl-4-MePh |
| | 1100 | Me | $N(CH_2CH_2OMe)_2$ | 2-Cl-4-MePh |
| | 1101 | Me | (S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe | 2-Cl-4-MePh |
| 15 | 1102 | Me | $N(c-C_3H_5)CH_2CH_2CN$ | 2,5-Me ₂ -4-MeOPh |
| | 1103 | Me | NEt ₂ | 2-Me-4-MeOPh |
| | 1104 | Me | OEt | 2-Me-4-MeOPh |
| | 1105 | Me | (S)-NHCH(CH ₂ CH ₂ OMe)CH ₂ OMe | 2-Me-4-MeOPh |
| | 1106 | Me | $N(c-C_3H_5)CH_2CH_2CN$ | 2-Me-4-MeOPh |
| 20 | 1107 | Me | NHCH(CH ₂ CH ₂ OEt) ₂ | 2-Me-4-MeOPh |
| | 1108 | Me | $N(c-C_3H_5)CH_2CH_2CN$ | 2,4-Cl ₂ -Ph |
| | 1109 | Me | NEt ₂ | 2-Me-4-ClPh |
| | 1110 | Me | NH-3-pentyl | 2-Me-4-ClPh |
| | 1111 | Me | $N(CH_2CH_2OMe)_2$ | 2-Me-4-ClPh |
| 25 | 1112 | Me | NHCH(CH ₂ OMe) ₂ | 2-Me-4-ClPh |
| | 1113 | Me | NEt ₂ | 2-Me-4-ClPh |
| | 1114 | Me | NEt ₂ | 2-Cl-4-MePh |
| | 1115 | Me | NH-3-pentyl | 2-Cl-4-MePh |
| | 1116 | Me | NHCH(CH ₂ OMe) ₂ | 2-Cl-4-MeOPh |
| 30 | 1117 | Me | $N(CH_2CH_2OMe)_2$ | 2-Cl-4-MeOPh |
| | 1118 | Me | NHCH(Et)CH ₂ OMe | 2-Cl-4-MeOPh |
| | 1119 | Me | $N(c-Pr)CH_2CH_2CN$ | 2-Cl-4-MeOPh |
| | 1120 | Me | NEt ₂ | 2-Cl-4-MeOPh |
| | 1121 | Me | NH-3-pentyl | 2-Cl-4-MeOPh |
| 35 | 1123 | Me | NHCH(Et)CH ₂ CH ₂ OMe | 2-Cl-4-MeOPh |
| | 1124 | Me | NHCH(Me)CH ₂ CH ₂ OMe | 2-Cl-4-MeOPh |

| | | | | |
|----|------|----|--|----------------------------------|
| | 1125 | Me | NHCH (Et) CH ₂ CH ₂ OMe | 2-Br-4-MeOPh |
| | 1126 | Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-Br-4-MeOPh |
| | 1127 | Me | NHCH (Et) CH ₂ CH ₂ OMe | 2-Me-4-MeOPh |
| | 1128 | Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-Me-4-MeOPh |
| 5 | 1129 | Me | NHCH (CH ₂ OMe) ₂ | 2-Cl-4, 5- (MeO) ₂ Ph |
| | 1130 | Me | N (CH ₂ CH ₂ OMe) ₂ | 2-Cl-4, 5- (MeO) ₂ Ph |
| | 1131 | Me | NHCH (Et) CH ₂ OMe | 2-Cl-4, 5- (MeO) ₂ Ph |
| | 1132 | Me | N (c-Pr) CH ₂ CH ₂ CN | 2-Cl-4, 5- (MeO) ₂ Ph |
| | 1133 | Me | NEt ₂ | 2-Cl-4, 5- (MeO) ₂ Ph |
| 10 | 1134 | Me | NH-3-pentyl | 2-Cl-4, 5- (MeO) ₂ Ph |
| | 1135 | Me | NHCH (Et) CH ₂ CH ₂ OMe | 2-Cl-4, 5- (MeO) ₂ Ph |
| | 1136 | Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-Cl-4, 5- (MeO) ₂ Ph |
| | 1137 | Me | NHCH (CH ₂ OMe) ₂ | 2-Br-4, 5- (MeO) ₂ Ph |
| | 1138 | Me | N (CH ₂ CH ₂ OMe) ₂ | 2-Br-4, 5- (MeO) ₂ Ph |
| 15 | 1139 | Me | NHCH (Et) CH ₂ OMe | 2-Br-4, 5- (MeO) ₂ Ph |
| | 1140 | Me | N (c-Pr) CH ₂ CH ₂ CN | 2-Br-4, 5- (MeO) ₂ Ph |
| | 1141 | Me | NEt ₂ | 2-Br-4, 5- (MeO) ₂ Ph |
| | 1142 | Me | NH-3-pentyl | 2-Br-4, 5- (MeO) ₂ Ph |
| | 1143 | Me | NHCH (CH ₂ OMe) ₂ | 2-Cl-4, 6- (MeO) ₂ Ph |
| 20 | 1144 | Me | N (CH ₂ CH ₂ OMe) ₂ | 2-Cl-4, 6- (MeO) ₂ Ph |
| | 1145 | Me | NEt ₂ | 2-Cl-4, 6- (MeO) ₂ Ph |
| | 1146 | Me | NH-3-pentyl | 2-Cl-4, 6- (MeO) ₂ Ph |
| | 1147 | Me | NHCH (CH ₂ OMe) ₂ | 2-Me-4, 6- (MeO) ₂ Ph |
| | 1148 | Me | N (CH ₂ CH ₂ OMe) ₂ | 2-Me-4, 6- (MeO) ₂ Ph |
| 25 | 1149 | Me | NHCH (Et) CH ₂ OMe | 2-Me-4, 6- (MeO) ₂ Ph |
| | 1150 | Me | NEt ₂ | 2-Me-4, 6- (MeO) ₂ Ph |
| | 1151 | Me | NH-3-pentyl | 2-Me-4, 6- (MeO) ₂ Ph |
| | 1152 | Me | NHCH (Et) CH ₂ CH ₂ OMe | 2-Me-4-MeOPh |
| | 1153 | Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-Me-4-MeOPh |
| 30 | 1154 | Me | NHCH (CH ₂ OMe) ₂ | 2-MeO-4-MePh |
| | 1155 | Me | N (CH ₂ CH ₂ OMe) ₂ | 2-MeO-4-MePh |
| | 1156 | Me | NHCH (Et) CH ₂ OMe | 2-MeO-4-MePh |
| | 1157 | Me | N (c-Pr) CH ₂ CH ₂ CN | 2-MeO-4-MePh |
| | 1158 | Me | NEt ₂ | 2-MeO-4-MePh |
| 35 | 1159 | Me | NH-3-pentyl | 2-MeO-4-MePh |
| | 1160 | Me | NHCH (Et) CH ₂ CH ₂ OMe | 2-MeO-4-MePh |

| | | | | |
|----|------|----|--|--------------|
| | 1161 | Me | NHCH (Me) CH ₂ CH ₂ OMe | 2-MeO-4-MePh |
| | 1162 | Me | NHCH (CH ₂ OMe) ₂ | 2-MeO-4-MePh |
| | 1163 | Me | N (CH ₂ CH ₂ OMe) ₂ | 2-MeO-4-MePh |
| | 1164 | Me | NHCH (Et) CH ₂ OMe | 2-MeO-4-MePh |
| 5 | 1165 | Me | N (c-Pr) CH ₂ CH ₂ CN | 2-MeO-4-MePh |
| | 1166 | Me | NEt ₂ | 2-MeO-4-MePh |
| | 1167 | Me | NH-3-pentyl | 2-MeO-4-MePh |
| | 1168 | Me | NHCH (CH ₂ OMe) ₂ | 2-MeO-4-ClPh |
| | 1169 | Me | N (CH ₂ CH ₂ OMe) ₂ | 2-MeO-4-ClPh |
| 10 | 1170 | Me | NHCH (Et) CH ₂ OMe | 2-MeO-4-ClPh |
| | 1171 | Me | NEt ₂ | 2-MeO-4-ClPh |
| | 1172 | Me | NH-3-pentyl | 2-MeO-4-ClPh |

15

Utility

20

CRF-R1 Receptor Binding Assay for the Evaluation of Biological Activity

25 The following is a description of the isolation of cell membranes containing cloned human CRF-R1 receptors for use in the standard binding assay as well as a description of the assay itself.

Messenger RNA was isolated from human hippocampus. The mRNA was reverse transcribed using oligo (dt) 12-18 and the coding region was amplified by PCR from start to stop codons. The resulting PCR fragment was cloned into the EcoRV site of pGEMV, from whence the insert was reclaimed using XhoI + XbaI and cloned into the XhoI + XbaI sites of vector pm3ar (which contains a CMV promoter, the SV40 't' splice and early poly A signals, an Epstein-Barr viral origin of replication, and a

hygromycin selectable marker). The resulting expression vector, called phchCRFR was transfected in 293EBNA cells and cells retaining the episome were selected in the presence of 400 μ M hygromycin. Cells surviving 4 weeks of selection in hygromycin were pooled, adapted to growth in suspension and used to generate membranes for the binding assay described below. Individual aliquots containing approximately 1×10^8 of the suspended cells were then centrifuged to form a pellet and frozen.

For the binding assay a frozen pellet described above containing 293EBNA cells transfected with hCRFR1 receptors is homogenized in 10 ml of ice cold tissue buffer (50 mM HEPES buffer pH 7.0, containing 10 mM $MgCl_2$, 2 mM EGTA, 1 μ g/l aprotinin, 1 μ g/ml leupeptin and 1 μ g/ml pepstatin). The homogenate is centrifuged at 40,000 x g for 12 min and the resulting pellet rehomogenized in 10 ml of tissue buffer. After another centrifugation at 40,000 x g for 12 min, the pellet is resuspended to a protein concentration of 360 μ g/ml to be used in the assay.

Binding assays are performed in 96 well plates; each well having a 300 μ l capacity. To each well is added 50 μ l of test drug dilutions (final concentration of drugs range from 10^{-10} - 10^{-5} M), 100 μ l of ^{125}I -ovine-CRF (^{125}I -o-CRF) (final concentration 150 pM) and 150 μ l of the cell homogenate described above. Plates are then allowed to incubate at room temperature for 2 hours before filtering the incubate over GF/F filters (presoaked with 0.3% polyethyleneimine) using an appropriate cell harvester. Filters are rinsed 2 times with ice cold assay buffer before removing individual filters and assessing them for radioactivity on a gamma counter.

Curves of the inhibition of ^{125}I -o-CRF binding to cell membranes at various dilutions of test drug are analyzed by the iterative curve fitting program LIGAND

[P.J. Munson and D. Rodbard, *Anal. Biochem.* 107:220 (1980), which provides K_i values for inhibition which are then used to assess biological activity.

A compound is considered to be active if it has a K_i value of less than about 10000 nM for the inhibition of CRF.

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

10 Inhibition of CRF-stimulated adenylate cyclase activity can be performed as described by G. Battaglia et al. *Synapse* 1:572 (1987). Briefly, assays are carried out at 37° C for 10 min in 200 ml of buffer containing 100 mM Tris-HCl (pH 7.4 at 37° C), 10 mM MgCl₂, 0.4 mM EGTA, 0.1% BSA, 1 mM isobutylmethylxanthine (IBMX), 250 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist peptides (concentration range 10⁻⁹ to 10⁻⁶m) and 0.8 mg original wet weight tissue (approximately 40-60 mg protein). Reactions are initiated by the addition of 1 mM ATP/[³²P]ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100 ml of 50 mM Tris-HCl, 45 mM ATP and 2% sodium dodecyl sulfate. In order to monitor the recovery of cAMP, 1 µl of [³H]cAMP (approximately 40,000 dpm) is added to each tube prior to separation. The separation of [³²P]cAMP from [³²P]ATP is performed by sequential elution over Dowex and alumina columns.

In vivo Biological Assay

The *in vivo* activity of the compounds of the present invention can be assessed using any one of the biological assays available and accepted within the art. Illustrative of these tests include the

Acoustic Startle Assay, the Stair Climbing Test, and the Chronic Administration Assay. These and other models useful for the testing of compounds of the present invention have been outlined in C.W. Berridge
5 and A.J. Dunn *Brain Research Reviews* 15:71 (1990). Compounds may be tested in any species of rodent or small mammal.

Compounds of this invention have utility in the
10 treatment of imbalances associated with abnormal levels of corticotropin releasing factor in patients suffering from depression, affective disorders, and/or anxiety.

Compounds of this invention can be administered
15 to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as
20 individual therapeutic agent or in combination of therapeutic agents. They can be administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard
25 pharmaceutical practice.

The dosage administered will vary depending on the use and known factors such as pharmacodynamic character of the particular agent, and its mode and route of administration; the recipient's age, weight,
30 and health; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and desired effect. For use in the treatment of said diseases or conditions, the compounds of this invention can be orally administered daily at a
35 dosage of the active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10

mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect.

Dosage forms (compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets and powders; or in liquid forms such as elixirs, syrups, and/or suspensions. The compounds of this invention can also be administered parenterally in sterile liquid dose formulations.

Gelatin capsules can be used to contain the active ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar-coated or film-coated to mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal tract.

Liquid dose forms for oral administration can contain coloring or flavoring agents to increase patient acceptance.

In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for

parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances.

- 5 Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain
- 10 preservatives such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences", A. Osol, a standard reference in the field.

- 15 Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

- 20 A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate.

25

Soft Gelatin Capsules

- A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is prepared and injected by means of a positive
- 30 displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

Tablets

- 35 A large number of tablets are prepared by conventional procedures so that the dosage unit was

100 mg active ingredient, 0.2 mg of colloidal silicon
dioxide, 5 mg of magnesium stearate, 275 mg of
microcrystalline cellulose, 11 mg of starch, and 98.8
mg lactose. Appropriate coatings may be applied to
5 increase palatability or delayed adsorption.

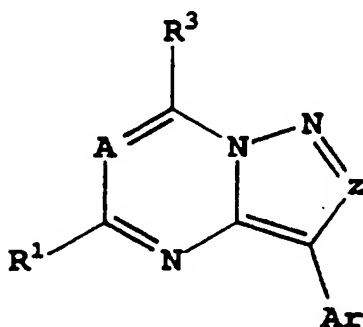
The compounds of this invention may also be used
as reagents or standards in the biochemical study of
neurological function, dysfunction, and disease.
10

Although the present invention has been
described and exemplified in terms of certain
preferred embodiments, other embodiments will be
apparent to those skilled in the art. The invention
15 is, therefore, not limited to the particular
embodiments described and exemplified, but is capable
of modification or variation without departing from
the spirit of the invention, the full scope of which
is delineated by the appended claims.
20

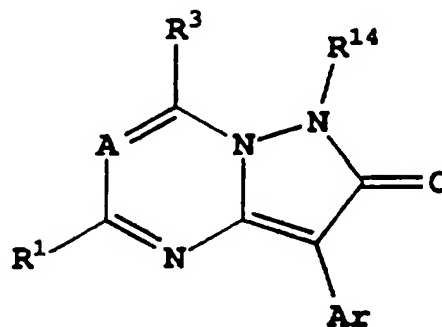
CLAIMS

WHAT IS CLAIMED IS:

- 5 1. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa
 10 or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and
 15 spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF,
 20 in mammals comprising administering to the mammal a therapeutically effective amount of a compound of Formulae (1) or (2):



(1)



(2)

25

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and

pharmaceutically acceptable salt or pro-drug forms thereof, wherein:

A is N or CR;

5

Z is N or CR²;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R⁴ groups and each Ar is attached to an unsaturated carbon atom;

10
15

R is independently selected at each occurrence from H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₇ cycloalkylalkyl, halo, CN, C₁-C₄ haloalkyl;

20

R¹ is independently selected at each occurrence from H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, halo, CN, C₁-C₄ haloalkyl, C₁-C₁₂ hydroxyalkyl, C₂-C₁₂ alkoxyalkyl, C₂-C₁₀ cyanoalkyl, C₃-C₆ cycloalkyl, C₄-C₁₀ cycloalkylalkyl, NR⁹R¹⁰, C₁-C₄ alkyl-NR⁹R¹⁰, NR⁹COR¹⁰, OR¹¹, SH or S(O)_nR¹²;

25

R² is selected from H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₀ cycloalkylalkyl, C₁-C₄ hydroxyalkyl, halo, CN, -NR⁶R⁷, NR⁹COR¹⁰, -NR⁶S(O)_nR⁷, S(O)_nNR⁶R⁷, C₁-C₄ haloalkyl, -OR⁷, SH or -S(O)_nR¹²;

30

35 R³ is selected from:

-H, OR⁷, SH, S(O)_nR¹³, COR⁷, CO₂R⁷,
 OC(O)R¹³, NR⁸COR⁷, N(COR⁷)₂, NR⁸CONR⁶R⁷,
 NR⁸CO₂R¹³, NR⁶R⁷, NR^{6a}R^{7a}, N(OR⁷)R⁶,
 CONR⁶R⁷, aryl, heteroaryl and heterocyclyl,
 5 or
 -C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₈ cycloalkyl, C₅-C₈ cycloalkenyl, C₄-
 C₁₂ cycloalkylalkyl or C₆-C₁₀
 cycloalkenylalkyl, each optionally
 10 substituted with 1 to 3 substituents
 independently selected at each occurrence
 from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo,
 C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³,
 15 NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl and heterocyclyl;

R⁴ is independently selected at each occurrence from:
 20 C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, NO₂,
 halo, CN, C₁-C₄ haloalkyl, NR⁶R⁷, NR⁸COR⁷,
 NR⁸CO₂R⁷, COR⁷, OR⁷, CONR⁶R⁷, CO(NOR⁹)R⁷, CO₂R⁷,
 or S(O)_nR⁷, where each such C₁-C₁₀ alkyl, C₂-
 25 C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl
 and C₄-C₁₂ cycloalkylalkyl are optionally
 substituted with 1 to 3 substituents
 independently selected at each occurrence from
 C₁-C₄ alkyl, NO₂, halo, CN, NR⁶R⁷, NR⁸COR⁷,
 30 NR⁸CO₂R⁷, COR⁷ OR⁷, CONR⁶R⁷, CO₂R⁷, CO(NOR⁹)R⁷,
 or S(O)_nR⁷;

R⁶ and R⁷, R^{6a} and R^{7a} are independently selected at
 each occurrence from:
 35 -H,

- 5 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
or C₆-C₁₄ cycloalkenylalkyl, each
optionally substituted with 1 to 3
substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-
10 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
heteroaryl or heterocyclyl,
15 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
heteroaryl(C₁-C₄ alkyl), heterocyclyl or
heterocyclyl(C₁-C₄ alkyl);
- alternatively, NR⁶R⁷ and NR^{6a}R^{7a} are independently
piperidine, pyrrolidine, piperazine, N-
20 methylpiperazine, morpholine or thiomorpholine, each
optionally substituted with 1-3 C₁-C₄ alkyl groups;
- R⁸ is independently selected at each occurrence from
H or C₁-C₄ alkyl;
25
- R⁹ and R¹⁰ are independently selected at each
occurrence from H, C₁-C₄ alkyl, or C₃-C₆
cycloalkyl;
- 30 R¹¹ is selected from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl,
or C₃-C₆ cycloalkyl;
- R¹² is C₁-C₄ alkyl or C₁-C₄ haloalkyl;
- 35 R¹³ is selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl,
C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-

C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-, heteroaryl or heteroaryl(C₁-C₄ alkyl)-;

- R¹⁴ is selected from C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₃-C₈ cycloalkyl, or C₄-C₁₂ cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, and C₁-C₆ alkylthio, C₁-C₆ alkylsulfinyl and C₁-C₆ alkylsulfonyl;
- R¹⁵ and R¹⁶ are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₄-C₁₆ cycloalkylalkyl, except that for S(O)_nR¹⁵, R¹⁵ cannot be H;
- aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, and CONR¹⁶R¹⁵;
- heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranal, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5

substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, -COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, and CONR¹⁶R¹⁵;

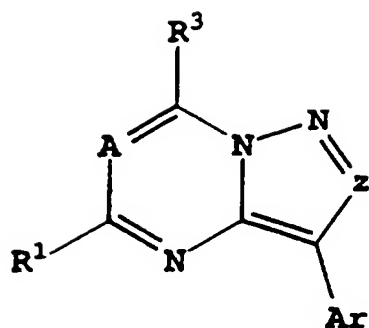
heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁵R¹⁶, and CONR¹⁶R¹⁵;

n is independently at each occurrence 0, 1 or 2,

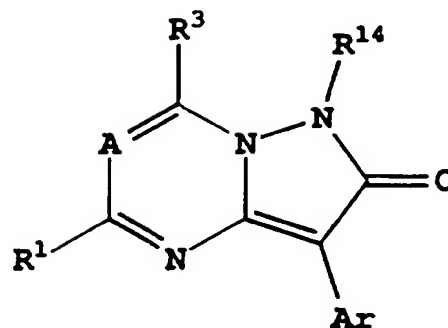
2. A method of claim 1 wherein, in the compound of Formulae (1) or (2), Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R⁴ substituents.

3. A method of claim 1 wherein, in the compound of Formulae (1) or (2), A is N, Z is CR², Ar is 2,4-dichlorophenyl, 2,4-dimethylphenyl or 2,4,6-trimethylphenyl, R¹ and R² are CH₃, and R³ is NR^{6a}R^{7a}.

4. A compound of Formulae (1) or (2):



(1)



(2)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and
 5 pharmaceutically acceptable salt or pro-drug forms thereof wherein:

A is N or CR;

10 Z is N or CR²;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-
 15 dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R⁴ groups and each Ar is attached to an unsaturated carbon atom;

20

R is independently selected at each occurrence from H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₇ cycloalkylalkyl, halo, CN, C₁-C₄ haloalkyl;

25

R¹ is independently selected at each occurrence from H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,

halo, CN, C₁-C₄ haloalkyl, C₁-C₁₂ hydroxyalkyl,
 C₂-C₁₂ alkoxyalkyl, C₂-C₁₀ cyanoalkyl, C₃-C₆
 cycloalkyl, C₄-C₁₀ cycloalkylalkyl, NR⁹R¹⁰, C₁-
 C₄ alkyl-NR⁹R¹⁰, NR⁹COR¹⁰, OR¹¹, SH or S(O)_nR¹²;

5 R² is selected from H, C₁-C₄ alkyl, C₂-C₄ alkenyl,
 C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₀
 cycloalkylalkyl, C₁-C₄ hydroxyalkyl, halo, CN,
 -NR⁶R⁷, NR⁹COR¹⁰, -NR⁶S(O)_nR⁷, S(O)_nNR⁶R⁷, C₁-
 10 C₄ haloalkyl, -OR⁷, SH or -S(O)_nR¹²;

R³ is selected from:

-H, OR⁷, SH, S(O)_nR¹³, COR⁷, CO₂R⁷,
 OC(O)R¹³, NR⁸COR⁷, N(COR⁷)₂, NR⁸CONR⁶R⁷,
 15 NR⁸CO₂R¹³, NR⁶R⁷, NR^{6a}R^{7a}, N(OR⁷)R⁶,
 CONR⁶R⁷, aryl, heteroaryl and
 heterocyclyl, or
 -C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₈ cycloalkyl, C₅-C₈ cycloalkenyl, C₄-
 20 C₁₂ cycloalkylalkyl or C₆-C₁₀
 cycloalkenylalkyl, each optionally
 substituted with 1 to 3 substituents
 independently selected at each occurrence
 from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo,
 25 C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³,
 NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl and heterocyclyl;

30 R⁴ is independently selected at each occurrence from:
 C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, NO₂,
 halo, CN, C₁-C₄ haloalkyl, NR⁶R⁷, NR⁸COR⁷,
 35 NR⁸CO₂R⁷, COR⁷, OR⁷, CONR⁶R⁷, CO(NOR⁹)R⁷, CO₂R⁷,

or $S(O)_nR^7$, where each such C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_6 cycloalkyl and C_4 - C_{12} cycloalkylalkyl are optionally substituted with 1 to 3 substituents

5 independently selected at each occurrence from C_1 - C_4 alkyl, NO_2 , halo, CN, NR^6R^7 , NR^8COR^7 , $NR^8CO_2R^7$, COR^7 OR⁷, $CONR^6R^7$, CO_2R^7 , $CO(NOR^9)R^7$, or $S(O)_nR^7$;

10 R^6 and R^7 , R^{6a} and R^{7a} are independently selected at each occurrence from:

-H,

- C_1 - C_{10} alkyl, C_3 - C_{10} alkenyl, C_3 - C_{10} alkynyl, C_1 - C_{10} haloalkyl with 1-10 halogens, C_2 - C_8 alkoxyalkyl, C_3 - C_6 cycloalkyl, C_4 -
15 C_{12} cycloalkylalkyl, C_5 - C_{10} cycloalkenyl, or C_6 - C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1 - C_6 alkyl, C_3 -
20 C_6 cycloalkyl, halo, C_1 - C_4 haloalkyl, cyano, OR¹⁵, SH, $S(O)_nR^{13}$, COR¹⁵, CO_2R^{15} , OC(O)R¹³, NR^8COR^{15} , $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl,
25 heteroaryl or heterocyclyl, -aryl, aryl(C_1 - C_4 alkyl), heteroaryl, heteroaryl(C_1 - C_4 alkyl), heterocyclyl or heterocyclyl(C_1 - C_4 alkyl),

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently
30 piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1 - C_4 alkyl groups;

R^8 is independently selected at each occurrence from
35 H or C_1 - C_4 alkyl;

R⁹ and R¹⁰ are independently selected at each occurrence from H, C₁-C₄ alkyl, or C₃-C₆ cycloalkyl;

5

R¹¹ is selected from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆ cycloalkyl;

R¹² is C₁-C₄ alkyl or C₁-C₄ haloalkyl;

10

R¹³ is selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-, heteroaryl or heteroaryl(C₁-C₄ alkyl)-;

15

R¹⁴ is selected from C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₃-C₈ cycloalkyl, or C₄-C₁₂ cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, and C₁-C₆ alkylthio, C₁-C₆ alkylsulfinyl and C₁-C₆ alkylsulfonyl;

20

25

R¹⁵ and R¹⁶ are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₄-C₁₆ cycloalkylalkyl, except that for S(O)_nR¹⁵, R¹⁵ cannot be H;

30

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at

35

each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano,

OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵,
 NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵,
 NR¹⁶R¹⁵, and CONR¹⁶R¹⁵;

5 heteroaryl is pyridyl, pyrimidinyl, triazinyl,
 furanyl, pyranyl, quinolinyl, isoquinolinyl,
 thienyl, imidazolyl, thiazolyl, indolyl,
 pyrrolyl, oxazolyl, benzofuranyl, benzothienyl,
 benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-
 10 dihydrobenzothienyl or 2,3-dihydrobenzofuranyl,
 each being optionally substituted with 1 to 5
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
 halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 15 S(O)_nR¹⁵, -COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵,
 N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, and
 CONR¹⁶R¹⁵;

heterocyclyl is saturated or partially saturated
 20 heteroaryl, optionally substituted with 1 to 5
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
 halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵,
 25 N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁵R¹⁶, and
 CONR¹⁶R¹⁵;

n is independently at each occurrence 0, 1 or 2,

30 with the provisos that:

(1) when A is N, Z is CR², R² is H, R³ is -OR⁷ or
 -OCOR¹³, and R⁷ is H, then R¹ is not H, OH or
 SH;

35

- 5 (2) when A is N, Z is CR², R¹ is CH₃ or C₂H₅, R² is H, and R³ is OH, H, CH₃, C₂H₅, C₆H₅, n-C₃H₇, i-C₃H₇, SH, SCH₃, NHC₄H₉, or N(C₂H₅)₂, then Ar is not phenyl or m-CH₃-phenyl;
- (3) when A is N, Z is CR², R² is H, and Ar is pyridyl, pyrimidinyl or pyrazinyl, and R³ is NR^{6a}R^{7a}, then R^{6a} and R^{7a} are not H or alkyl;
- 10 (4) when A is N, Z is CR², and R² is SO₂NR⁶R⁷, then R³ is not OH or SH;
- (5) when A is CR and Z is CR², then R² is not-NR⁶SO₂R⁷ or -SO₂NR⁶R⁷;
- 15 (6) when A is N, Z is CR² and R² is -NR⁶SO₂R⁷ or -SO₂NR⁶R⁷, then R³ is not OH or SH;
- (7) when A is N, Z is CR², R¹ is methyl or ethyl, R² is H, and R³ is H, OH, CH₃, C₂H₅, C₆H₅, n-C₃H₇, iso-C₃H₇, SH, SCH₃, NH(n-C₄H₉), or N(C₂H₅)₂, then Ar is not unsubstituted phenyl or m-methylphenyl;
- 20 (8) when A is CR, Z is CR², R² is H, phenyl or alkyl, R³ is NR⁸COR⁷ and Ar is phenyl or phenyl substituted with phenylthio, then R⁷ is not aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄ alkyl);
- 25 (9) when A is CR, Z is CR², R² is H or alkyl, Ar is phenyl, and R³ is SR¹³ or NR^{6a}R^{7a}, then R¹³ is not aryl or heteroaryl and R^{6a} and R^{7a} are not H or aryl; or
- 30 (10) when A is CH, Z is CR², R¹ is OR¹¹, R² is H, R³ is OR⁷, and R⁷ and R¹¹ are both H, then Ar is not
- 35

phenyl, p-Br-phenyl, p-Cl-phenyl, p-NHCOCH₃-phenyl, p-CH₃-phenyl, pyridyl or naphthyl;

5 (11) when A is CH, Z is CR², R² is H, Ar is unsubstituted phenyl, and R³ is CH₃, C₂H₅, CF₃ or C₆H₄F, then R₁ is not CF₃ or C₂F₅;

(12) when A is CR, R is H, Z is CR², R² is OH, and R¹ and R³ are H, then Ar is not phenyl;

10

(13) when A is CR, R is H, Z is CR², R² is OH or NH₂, R¹ and R³ are CH₃, then Ar is not 4-phenyl-3-cyano-2-aminopyrid-2-yl.

15 5. A compound of claim 4 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof with the additional provisos that: (1) when A is N, R¹ is H,
20 C₁-C₄ alkyl, halo, CN, C₁-C₁₂ hydroxyalkyl, C₁-C₄ alkoxyalkyl or SO₂(C₁-C₄ alkyl), R³ is NR^{6a}R^{7a} and R^{6a} is unsubstituted C₁-C₄ alkyl, then R^{7a} is not phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl,
25 benzothiazolyl, indolyl or C₃-C₆ cycloalkyl; and (2) A is N, R¹ is H, C₁-C₄ alkyl, halo, CN, C₁-C₁₂ hydroxyalkyl, C₁-C₄ alkoxyalkyl or SO₂(C₁-C₄ alkyl), R³ is NR^{6a}R^{7a} and R^{7a} is unsubstituted C₁-C₄ alkyl, then R^{6a} is not phenyl, naphthyl, thienyl,
30 benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, indolyl or C₃-C₆ cycloalkyl.

6. A compound of claim 4 and isomers thereof,
35 stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically

acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R⁴ substituents.

- 5 7. A compound of claim 6 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is N, Z is CR², Ar is 2,4-dichlorophenyl, 2,4-
10 dimethylphenyl or 2,4,6-trimethylphenyl, R¹ and R² are CH₃, and R³ is NR^{6a}R^{7a}.
8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutical-
15 ly effective amount of a compound of claim 4.
9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutical-
20 ly effective amount of a compound of claim 6.
10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutical-
ly effective amount of a compound of claim 7.
- 25 11. A compound of claim 4 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is N.
30
12. A compound of Formula (2) of claim 11 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.
35

13. A compound of claim 12 and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein Ar is
5 phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar
is optionally substituted with 1 to 4 R⁴ substituents.
14. A compound of claim 12 and isomers thereof,
stereoisomeric forms thereof, or mixtures of
10 stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein R³ is
NR^{6a}R^{7a} or OR⁷.
15. A compound of claim 12 and isomers thereof,
15 stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein Ar is
phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar
is optionally substituted with 1 to 4 R⁴ substituents,
20 and R³ is NR^{6a}R^{7a} or OR⁷.
16. A compound of Formula (1) of claim 11 and isomers
thereof, stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
25 acceptable salt or pro-drug forms thereof wherein Z is
CR².
17. A compound of claim 16 and isomers thereof,
stereoisomeric forms thereof, or mixtures of
30 stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein Ar is
phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar
is optionally substituted with 1 to 4 R⁴ substituents.
- 35 18. A compound of claim 16 and isomers thereof,
stereoisomeric forms thereof, or mixtures of

stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R³ is NR^{6a}R^{7a} or OR⁷.

- 5 19. A compound of claim 18 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

- 10 -H,
-C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
15 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
or C₆-C₁₄ cycloalkenylalkyl, each
optionally substituted with 1 to 3
substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-
20 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
heteroaryl or heterocyclyl,
25 -aryl, aryl(C₁-C₄ alkyl)-, heteroaryl,
heteroaryl(C₁-C₄ alkyl)-, heterocyclyl or
heterocyclyl(C₁-C₄ alkyl)-; and

R^{7a} is independently selected at each occurrence from:

- H,
30 -C₅-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
or C₆-C₁₄ cycloalkenylalkyl, each
optionally substituted with 1 to 3
35 substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-

- C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 5 heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 heterocyclyl(C₁-C₄ alkyl);
- 10 alternatively, NR⁶R⁷ and NR^{6a}R^{7a} are independently
 piperidine, pyrrolidine, piperazine, N-
 methylpiperazine, morpholine or thiomorpholine, each
 optionally substituted with 1-3 C₁-C₄ alkyl groups.
- 15 20. A compound of claim 18 and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein R^{6a}
 and R^{7a} are identical and are selected from:
- 20 -C₁-C₄ alkyl or C₃-C₆ cycloalkyl, each optionally
 substituted with 1 to 3 substituents
 independently selected at each occurrence from
 C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
 haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, -COR¹⁵,
 25 CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
 aryl, heteroaryl or heterocyclyl, and
 -aryl or heteroaryl.
- 30 21. A compound of claim 18 and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein
 R^{6a} is selected from:
- 35 -H,

5 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 10 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-
 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 15 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
 20 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 heterocyclyl(C₁-C₄ alkyl);

R^{7a} is selected from:

-C₁-C₄ alkyl and each such C₁-C₄ alkyl is
 substituted with 1-3 substituents
 20 independently selected at each occurrence from
 C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
 haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,
 CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
 25 aryl, heteroaryl or heterocyclyl.

22. A compound of claim 18 and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 30 acceptable salt or pro-drug forms thereof wherein
 one of R^{6a} and R^{7a} is selected from:

-C₃-C₆ cycloalkyl, each such C₃-C₆ cycloalkyl
 optionally substituted with 1-3 substituents
 independently selected at each occurrence from
 35 C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
 haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,

CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
 aryl, heteroaryl or heterocyclyl,

-aryl,

5 -heteroaryl or

-heterocyclyl,

and the other of R^{6a} and R^{7a} is unsubstituted C₁-C₄
 alkyl.

10 23. A compound of claim 18 and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein
 R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl,
 15 each such C₁-C₁₀ alkyl optionally substituted with
 1 to 3 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
 halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³,
 COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 20 R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl.

24. A compound of claim 16 and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 25 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein Ar is
 phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar
 is optionally substituted with 1 to 4 R⁴ substituents,
 and R³ is NR^{6a}R^{7a} or OR⁷.

30

25. A compound of claim 24 and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein
 35 R^{6a} is independently selected from:

-H,

- 5 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
or C₆-C₁₄ cycloalkenylalkyl, each
optionally substituted with 1 to 3
substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-
C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
10 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
heteroaryl or heterocyclyl,
-aryl, aryl(C₁-C₄ alkyl)-, heteroaryl,
15 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
heterocyclyl(C₁-C₄ alkyl);
R^{7a} is independently selected at each occurrence from:
-H,
20 -C₅-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
or C₆-C₁₄ cycloalkenylalkyl, each
optionally substituted with 1 to 3
25 substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-
C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
30 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
heteroaryl or heterocyclyl,
-aryl, aryl(C₁-C₄ alkyl), heteroaryl,
heteroaryl(C₁-C₄ alkyl), heterocyclyl or
heterocyclyl(C₁-C₄ alkyl),
35

alternatively, NR^{6R7} and NR^{6aR7a} are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C₁-C₄ alkyl groups.

5

26. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:

10

-C₁-C₄ alkyl or C₃-C₆ cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, -COR¹⁵,
15 CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR^{16R15}, NR⁸CO₂R¹³, NR^{16R15}, CONR^{16R15}, aryl, heteroaryl or heterocyclyl, and
-aryl or heteroaryl.

15

20

27. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are

25

-C₁-C₄ alkyl, each such C₁-C₄ alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
30 S(O)_nR¹³, -COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR^{16R15}, NR⁸CO₂R¹³, NR^{16R15}, CONR^{16R15}, aryl, heteroaryl or heterocyclyl.

30

28. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein
 5 R_{6a} is selected from:

-H,
 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 10 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl, or C₆-C₁₄ cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-
 15 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl,
 20 -aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄ alkyl);

R_{7a} is:

-C₁-C₄ alkyl and each such C₁-C₄ alkyl is
 25 substituted with 1-3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
 30 NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

29. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of
 35 stereoisomeric forms thereof, and pharmaceutically

acceptable salt or pro-drug forms thereof wherein one of R^{6a} and R^{7a} is selected from:

- C₃-C₆ cycloalkyl, each such C₃-C₆ cycloalkyl
optionally substituted with 1-3 substituents
independently selected at each occurrence from
C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵,
CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
aryl, heteroaryl or heterocyclyl,
-aryl,
-heteroaryl or
-heterocyclyl,
and the other of R^{6a} and R^{7a} is unsubstituted C₁-C₄
alkyl.

30. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl, each such C₁-C₁₀ alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

31. A compound of claim 16 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein
-Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl,
and each Ar is optionally substituted with 1 to 4 R⁴ substituents,

- R³ is NR^{6a}R^{7a} or OR⁷ and
-R¹ and R² are independently selected from H, C₁-C₄
alkyl, C₃-C₆ cycloalkyl, C₄-C₁₀
cycloalkylalkyl.

5

32. A compound of claim 31 and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein
10 R^{6a} is independently selected from:

- H,
-C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
15 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
or C₆-C₁₄ cycloalkenylalkyl, each
optionally substituted with 1 to 3
substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-
20 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
heteroaryl or heterocyclyl,
25 -aryl, aryl(C₁-C₄ alkyl)-, heteroaryl,
heteroaryl(C₁-C₄ alkyl), heterocyclyl or
heterocyclyl(C₁-C₄ alkyl);

R^{7a} is independently selected at each occurrence from:

- H,
30 -C₅-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
or C₆-C₁₄ cycloalkenylalkyl, each
35 optionally substituted with 1 to 3
substituents independently selected at each

occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl, -aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄ alkyl),

10

alternatively, NR⁶R⁷ and NR^{6a}R^{7a} are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C₁-C₄ alkyl groups.

15

33. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:

-C₁-C₄ alkyl or C₃-C₆ cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, -COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl, and -aryl or heteroaryl.

30

34. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are

35

- 5 -C₁-C₄ alkyl, each such C₁-C₄ alkyl
 optionally substituted with 1 to 3
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
 halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH,
 S(O)_nR¹³, -COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵,
 N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵,
 CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.
- 10 35. A compound of claim 31 and isomers thereof,
 stereoisomeric forms thereof, or mixtures of
 stereoisomeric forms thereof, and pharmaceutically
 acceptable salt or pro-drug forms thereof wherein
 R^{6a} is selected from:
- 15 -H,
 -C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl,
 C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈
 alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
 C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl,
 or C₆-C₁₄ cycloalkenylalkyl, each
 optionally substituted with 1 to 3
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-
 C₆ cycloalkyl, halo, C₁-C₄ haloalkyl,
 cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵,
 OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵,
 NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
 heteroaryl or heterocyclyl,
 -aryl, aryl(C₁-C₄ alkyl), heteroaryl,
 heteroaryl(C₁-C₄ alkyl), heterocyclyl or
 heterocyclyl(C₁-C₄ alkyl);
- 20 R^{7a} is:
- 25 -C₁-C₄ alkyl and each such C₁-C₄ alkyl is
 substituted with 1-3 substituents
 independently selected at each occurrence from
 C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
- 30 35

haloalkyl, cyano, OR¹⁵, SH, S(O)nR¹³, COR¹⁵,
CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
aryl, heteroaryl or heterocyclyl.

5

36. A compound of claim 31 and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein one of
10 R^{6a} and R^{7a} is selected from:

-C₃-C₆ cycloalkyl, each such C₃-C₆ cycloalkyl
optionally substituted with 1-3 substituents
independently selected at each occurrence from
C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄
15 haloalkyl, cyano, OR¹⁵, SH, S(O)nR¹³, COR¹⁵,
CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,
NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵,
aryl, heteroaryl or heterocyclyl,

-aryl,

20

-heteroaryl or

-heterocyclyl,

and the other of R^{6a} and R^{7a} is unsubstituted C₁-C₄
alkyl.

25

37. A compound of claim 31 and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof wherein
R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl,

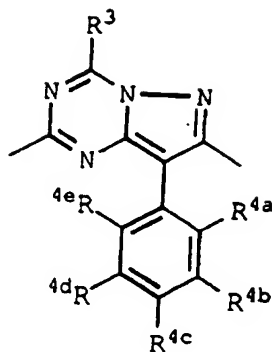
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each such C₁-C₁₀ alkyl optionally substituted with
1 to 3 substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)nR¹³,
COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂,

35

R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl,
heteroaryl or heterocyclyl.

38. A compound of claim 31 of Formula (50)



5

FORMULA (50)

- and isomers thereof, stereoisomeric forms thereof, or
 10 mixtures of stereoisomeric forms thereof, and
 pharmaceutically acceptable salt or pro-drug forms
 thereof, selected from the group consisting of:
- 15 a compound of Formula (50) wherein R^3 is $-\text{NHCH}(\text{n-Pr})_2$,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is
 H;
- 20 a compound of Formula (50) wherein R^3 is $-\text{N}(\text{Et})(\text{n-Bu})$,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is
 H;
- 25 a compound of Formula (50) wherein R^3 is $-(\text{n-Pr})(\text{CH}_2\text{cPr})$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is
 H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $-\text{N}(\text{CH}_2\text{CH}_2\text{OMe})_2$,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is
 H;
- 30 a compound of Formula (50) wherein R^3 is $-\text{NHCH}(\text{Et})(\text{n-Bu})$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and
 R^{4e} is H;

- a compound of Formula (50) wherein R^3 is
-NHCH(Et)(CH₂OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl,
 R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is -NHCH(CH₂OMe)₂,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is
H;
- 10 a compound of Formula (50) wherein R^3 is -N(Et)₂, R^{4a} is
Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is -NHCH(CH₂OEt)₂,
 R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is
H;
- 15 a compound of Formula (50) wherein R^3 is -NHCH(Et)₂, R^{4a}
is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is -N(Me)(Ph), R^{4a}
is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is -N(n-Pr)₂, R^{4a}
is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is -NHCH(Et)(n-
Pr), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and
 R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is -NHCH(CH₂OMe)₂,
 R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is
Me;
- a compound of Formula (50) wherein R^3 is -NHCH(CH₂OMe)₂,
 R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is
H;
- 35 a compound of Formula (50) wherein R^3 is -N(CH₂CH₂OMe)₂,
 R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is
H;
- 40 a compound of Formula (50) wherein R^3 is
-NHCH(Et)(CH₂OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me,
 R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (50) wherein R^3 is -NHCH(Et)₂, R^{4a}
is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $-OEt$, R^{4a} is Cl , R^{4b} is H , R^{4c} is Cl , R^{4d} is H and R^{4e} is H ;
- 5 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is H ;
- a compound of Formula (50) wherein R^3 is $-N(CH_2CN)_2$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is H ;
- 10 a compound of Formula (50) wherein R^3 is $-NHCH(Me)(CH_2OMe)$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is H ;
- 15 a compound of Formula (50) wherein R^3 is $-OCH(Et)(CH_2OMe)$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is H ;
- 20 a compound of Formula (50) wherein R^3 is $-N(n-Pr)(CH_2cPr)$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is H ;
- a compound of Formula (50) wherein R^3 is $-NHCH(Me)(CH_2N(Me)_2)$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is H ;
- 25 a compound of Formula (50) wherein R^3 is $-N(cPr)(CH_2CH_2CN)$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is H ;
- 30 a compound of Formula (50) wherein R^3 is $-N(n-Pr)(CH_2CH_2CN)$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is H ;
- 35 a compound of Formula (50) wherein R^3 is $-N(n-Bu)(CH_2CN)$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is H ;
- 40 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is Me ;
- 45 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me , R^{4b} is H , R^{4c} is Me , R^{4d} is H and R^{4e} is Me ;

- a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 5 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OEt)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 20 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2CH_2OMe)(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;
- 25 a compound of Formula (50) wherein R^3 is morpholino, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NH(c-Pr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is CN, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

- 5 a compound of Formula (50) wherein R^3 is $-NCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- 25 a compound of Formula (50) wherein a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is (S)- $NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $-NH(CH_2OMe)(CH_2-iPr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is H, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe_2 , R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(n-Pr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OEt)(Et)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe_2 , R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 45

- a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe_2 , R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is (S)- $NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is (S)- $NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $-NH(Et)(CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)(CH_2CH_2OH)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (50) wherein R^3 is $-N(CH_2c-Pr)(n-Pr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 45 a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is CN, R^{4d} is H and R^{4e} is H;

- a compound of Formula (50) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OH)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H; and
- 10 a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H
- 15 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H; and
- 20 a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H.
39. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein
- 25 said compound is 4-(bis-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.
40. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein
- 30 said compound is 4-(bis-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2,5-dimethyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.
- 35 41. A compound of claim 4 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically

acceptable salt or pro-drug forms thereof wherein A is CR.

42. A compound of Formula (2) of claim 41 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

43. A compound of claim 42 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R⁴ substituents.

44. A compound of claim 42 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R³ is NR^{6a}R^{7a} or OR⁷.

45. A compound of claim 42 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R⁴ substituents, and R³ is NR^{6a}R^{7a} or OR⁷.

46. A compound of Formula (1) of claim 41 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Z is CR².

47. A compound of claim 46 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R⁴ substituents.
48. A compound of claim 46 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R³ is NR^{6a}R^{7a} or OR⁷.
49. A compound of claim 46 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R⁴ substituents, and R³ is NR^{6a}R^{7a} or OR⁷.
50. A compound of claim 49 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl, and each such C₁-C₁₀ alkyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.
51. A compound of claim 46 and isomers thereof, stereoisomeric forms thereof, or mixtures of

stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein

-Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1

5 to 4 R⁴ substituents,

-R³ is NR^{6a}R^{7a} or OR⁷ and

-R¹ and R² are independently selected from H, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₄-C₁₀ cycloalkylalkyl.

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52. A compound of claim 51 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein

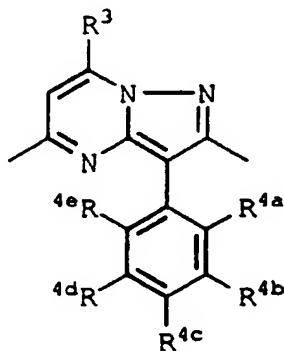
15 R^{6a} and R^{7a} are independently H or C₁-C₁₀ alkyl, and each such C₁-C₁₀ alkyl is optionally

substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵,

20 SH, S(O)_nR¹³, COR¹⁵, CO₂R¹⁵, OC(O)R¹³, NR⁸COR¹⁵, N(COR¹⁵)₂, R⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹³, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl.

53. A compound of claim 51 of Formula (51)

25



FORMULA (51)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof selected from the group consisting of:

- 5 a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
10
- a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
25
- a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
30
- a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(n-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
40
- a compound of Formula (51) wherein R^3 is $-N(n-Bu)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

- a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$,
10 R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is (S)
 $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is
 $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NH(Et)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$,
 R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is (S)
 $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is
40 $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(n-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 45

- a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (51) wherein R^3 is (S)
 $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 10 a compound of Formula (51) wherein R^3 is
 $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is $-N(c-Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) wherein R^3 is $-NHCH(n-Pr)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 45

- a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 5 a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;
- 10 a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 15 a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 20 a compound of Formula (51) wherein R^3 is $-N(Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-N(Bu)(Et)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 25 a compound of Formula (51) wherein R^3 is $-NHCH(Et)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 30 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- 35 a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;
- a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;
- 40 a compound of Formula (51) wherein R^3 is $-NEt_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;
- 45 and

a compound of Formula (51) wherein R³ is
-N(Pr)(CH₂CH₂CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe,
R^{4d} is H and R^{4e} is H.

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54. A compound of claim 51 and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof, wherein
10 said compound is 7-(3-pentylamino)-2,5-dimethyl-3-(2-
methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine.

55. A compound of claim 51 and isomers thereof,
stereoisomeric forms thereof, or mixtures of
15 stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof, wherein
said compound is 7-(Diethylamino)-2,5-dimethyl-3-(2-
methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine.

20 56. A compound of claim 51 and isomers thereof,
stereoisomeric forms thereof, or mixtures of
stereoisomeric forms thereof, and pharmaceutically
acceptable salt or pro-drug forms thereof, wherein
said compound is 7-(N-(3-cyanopropyl)-N-propylamino)-
25 2,5-dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-
pyrazolopyrimidine.

57. A pharmaceutical composition comprising a
pharmaceutically acceptable carrier and a therapeutical-
30 ly effective amount of a compound of claim 4.

58. A pharmaceutical composition comprising a
pharmaceutically acceptable carrier and a therapeutical-
ly effective amount of a compound of claim 24.
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59. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 38.

60. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 39.

61. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 40.

62. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 53.

63. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 54.

64. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 55.

65. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 56.

66. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility

problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 4.

67. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 24.

68. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or

alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 38.

69. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 39.

70. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's

disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 40.

71. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 53.

72. A method of treating affective disorder, anxiety, depression, headache, irritable bowel

syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 54.

73. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 55.

74. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 56.

INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/US 97/13072

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D487/04 A61K31/505 //(C07D487/04,239:00,231:00),
(C07D487/04,251:00,231:00),(C07D487/04,249:00,239:00),
(C07D487/04,251:00,249:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

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